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# STEREOCHEMICAL STUDIES OF 1,2-DIAMINOCYCLOHEXANE AND SOME OF ITS DERIVATIVES

SACHIKO ITO HOWARD
*University of New Hampshire, Durham*

Howard, Sachiko Ito

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# STEREOCHEMICAL STUDIES OF 1,2-DIAMINOCYCLOHEXANE AND SOME OF ITS DERIVATIVES

BY

Sachiko Ito Howard
B.A., Harvard University, 1966

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This dissertation has been examined and approved.

James D. Morrison

Dissertation director, James D. Morrison
Professor of Chemistry

Alexander R. Amell, Professor of Chemistry

Paul R. Jones

Paul R. Jones, Professor of Chemistry

Gary R. Weisman

Gary R. Weisman, Associate Professor of Chemistry

Thomas G. Pistole

Thomas G. Pistole, Professor of Microbiology

Nov. 20, 1984

Date

TO ROB, FISH AND BEN

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

STEREOCHEMICAL STUDIES OF 1,2-DIAMINOCYCLOHEXANE AND SOME OF ITS DERIVATIVES

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The literature methods for the determination of chemical purity and ratio of cis and trans diastereoisomers of 1,2-diaminocyclohexane (DACH) from commercial sources were evaluated. Carbon-13 nuclear magnetic resonance spectroscopy was found to be most convenient for routine analysis. Gas chromatographic analysis after the Eschweiler-Clarke N-methylation was found to give a faulty isomer ratio unless special precautions were taken to insure complete reaction, since the cis isomer was found to undergo unusually slow conversion to its tetramethyl derivative compared to the rate of conversion of the trans isomer.

Optically active cis-2,3-diphenyldecahydroquinoxaline and trans-2,3-diphenyldecahydroquinoxaline were prepared by stereoselective reductions of 2,3-diphenylhexahydroquinoxaline obtained by the condensation of benzil and (-)-(R,R)-DACH enantiomer. Optically active N,N'-dibenzyl-1,2-diaminocyclohexane (DBDACH) was prepared by the $NaBH_4$ reduction of the diimine obtained by the condensation of benzaldehyde and (-)-(R,R)-DACH enantiomer.

Three diamines were added to suspensions of lithium aluminum hydride (LAH) in ether to produce chirally modified LAH reagents.

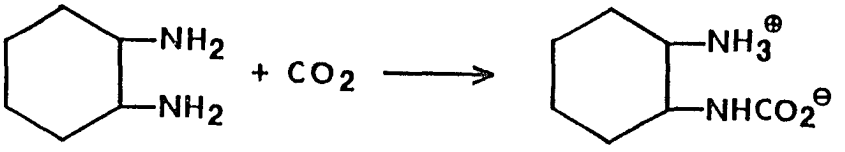
Propiophenone was reduced to (R)-1-phenylethanol in 36% enantiomeric excess (e.e.) by the DBDACH-LAH reagent. The reduction of propiophenone by LAH reagents modified with the two chiral decahydroquinoxalines resulted in carbinol with (S)-configuration but with small asymmetric inductions (less than 5% e.e.).

## I: PROPERTIES AND APPLICATIONS OF 1,2-DIAMINOCYCLOHEXANE

1,2-Diaminocyclohexane (DACH) is a well-known compound[1] which has physical and chemical properties typical of low molecular weight aliphatic primary diamines. It has an unpleasant ammoniacal odor, readily dissolves in water, and reacts with $CO_2$ in air to form a white solid "carbonate" (Fig. 1). Unless protected from light and stored in a cold place, DACH darkens upon standing.*

Figure 1

Reaction of DACH with $CO_2$



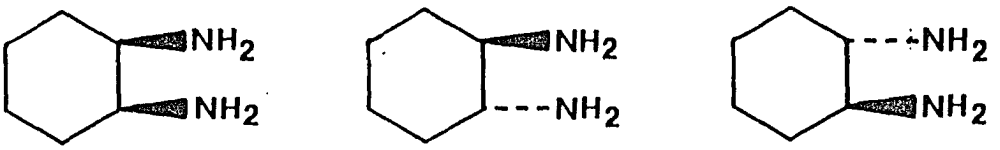

There are three stereoisomers of DACH (Fig. 2): achiral cis-DACH (1) and a pair of trans-DACH enantiomers (2 and 3). The absolute configurations of the trans-DACH enantiomers were first inferred from circular dichroism (CD) and optical rotatory dispersion (ORD) studies,[2-4] and the assignments were later confirmed by an X-ray diffraction study of a DACH-Co(III) complex.[5] Some physical

* It is reported that amines distilled from small amounts of sodium borohydride resist discoloration and have longer shelf-life (Ref 6), but this procedure has not been applied to DACH by this author and the effectiveness of such a procedure for DACH is not reported.

properties of DACH are listed in Table 1.

Figure 2

Stereoisomers of DACH




1 2 3

| cis-1,2-diaminocyclohexane | (-)-(R,R)-trans-1,2-diaminocyclohexane | (+)-(S,S)-trans-1,2-diaminocyclohexane |
|---|---|---|
| cis-DACH | (-)-DACH | (+)-DACH |

Commercial Sources of DACH

DACH is available from various commercial sources in packages ranging from laboratory to large bulk (tank car) quantities. It can be purchased both as a mixture of cis and trans isomers and as pure trans-DACH (racemic or optically active). The chemical purity of DACH samples and the isomer ratio of DACH mixtures vary widely, however, depending on the supplier and even upon lot variations from a single supplier. Although the quality of a commercial DACH mixture ranges from poor to excellent, the unit cost is nearly uniform among six major DACH suppliers. The names and addresses of the DACH suppliers and the current prices (as of April, 1984) are given in Table 2.

Table 1

Physical Properties of DACH

| | mp: | bp: | sp gr at 20°: | specific rotation $[\alpha]_D$: | pK:[j] |
|---|---|---|---|---|---|
| cis-DACH | 2°[a] | 39-41°/2mm[g] | | | $pK_1$: 9.93 |
| | 6°[b] | 92-93°/18mm[h] | | | $pK_2$: 6.13 |
| | | 183°[a] | | | |
| (±)-trans-DACH | 14.8°[c] | 41-42.2°/2mm[g] | 0.94[e] | | $pK_1$: 9.94 |
| | 19-20°[d] | 79-80°/12mm[d] | | | $pK_2$: 6.47 |
| | 20-21°[e] | 188°[e] | | | |
| (+)- or (-)-trans-DACH | 42.7°[c] | 71-73°/8mm[f] | | 41.5°(c5.23, benzene)[f] | |
| | 44°[f] | | | 44.1°(c3, methanol)[i] | |

[a]Ref 7. [b]Ref 8. [c]Ref 9. [d]Ref 10.

[e]Ref 11. [f]Ref 12. [g]Ref 13. [h]Ref 14.

[i]Ref 15. [j]$pK_1$: $pK_a$ for DACH·$H^+$; $pK_2$: $pK_a$ for DACH·$2H^+$; Ref 16.

Table 2

DACH Suppliers

| | | |
|---|---|---|
| 1. | The Ames Laboratories, Inc.<br>C/T: $15/100g | P. O. Box 3024<br>200 Rock Lane<br>Milford, CT 06460<br>203-874-2463 |
| 2. | Alfa Products,<br>Thiokol/Ventron Div.<br>C/T: $13/250g<br>-T: $26/g<br>+T: $49/g | 152 Andover St.<br>Danvers, MA 01923<br>617-777-1970 |
| 3. | Aldrich Chemical Co., Inc.<br>C/T: $31.65/kg<br>T: $37/250mL | 940 W. St. Paul Ave.<br>Milwaukee, WI 53233<br>414-273-3850 |
| 4. | ICN K&K Laboratories<br>C/T: $225/250g | 121 Express St.<br>Plainview, NY 11803<br>516-433-6262 |
| 5. | Fluka Chemical Corp.<br>C/T: $22.50/liter | 255 Osser Ave.<br>Hauppague, NY 11787<br>516-273-0110 |
| 6. | Lachat Chemicals, Inc. | 10500 N. Port Washignton Rd.<br>Mequon, WI 53092<br>414-241-3872 |
| 7. | Pfaltz & Bauer, Inc.<br>Div. of Aceto Chemical Co.<br>C/T: $22/kg | 375 Fairfield Ave.<br>Stamford, CT 06902<br>203-357-8700 |
| 8. | Strem Chemicals, Inc.<br>T: $60/250g<br>-T: $26/g | 7 Mulliken Way<br>P. O. Box 108<br>Newburyport, MA 01950<br>617-462-3191 |

| | | |
|---|---|---|
| 9. | Chemical Dynamics Corp. | P. O. Box 395<br>Hadley Rd.<br>South Plainfield, NJ 07080<br>201-753-5000 |
| 10. | Chemicals Procurement Labs, Inc.<br>C/T: $825/kg | 18-17 130th St.<br>P. O. Box 75<br>College Point, NY 11356<br>212-353-2663 |
| 11. | E.I.DuPont de Nemours & Co. Petrochemicals Department; Polymer Intermediates Div.<br>C/T: 75¢/lb, 55 gal min. | 1007 Market St.<br>Wilmington, DE 19898<br>302-774-2421 |
| 12. | Overlook Industries, Inc. Sapon Laboratories Div.<br>T: $41/10g | 511 RD #1<br>Bloomsbury, NJ 08804<br>201-454-1000 |
| 13. | Sharpe Chemicals Co.<br>C/T: $42.50/kg | 1116 South Varney St.<br>Burbank, CA 91502<br>213-841-7605 |
| 14. | Oxid, Inc.<br>T: $22.50/lb | 101 Concrete St.<br>Houston, Texas 77012<br>713-923-9136 |
| 15. | CTC Organics<br>C/T: $135/500mL | P.O. Box 6933<br>Atlanta, GA<br>404-524-6744 |

C/T: cis-trans mixture

T: racemic trans-DACH

-T: (-)-trans-DACH

+T: (+)-trans-DACH

cis-DACH is not commercially available.

The wide variation in the quality of the commercial DACH samples is associated with the origin of these materials. The main source of commercial DACH is the by-product stream from the production of hexamethylenediamine (HMDA) by the catalytic hydrogenation of adiponitrile. HMDA is produced in large quantities for the manufacture of Nylon 66.[12, 17-19] The composition of this by-product stream varies from one run to the next and from one plant to the next.[7] The crude material is sold to the supplier to be treated according to its custom for retail sales. Sometimes the sample is sold after a simple distillation; sometimes it is purified under rigorous conditions. For example, Oxid recently introduced highly purified trans-DACH (racemic) to the market, which has been prepared by a freeze-thaw method after an initial purification by distillation.[20]

The quality of DACH samples is not obvious from a cursory examination of suppliers' data sheets. The author has found that often the data provided are quite inaccurate. The analyses of commercial DACH samples and a critical evaluation of various analytical methods are discussed in Section II of this thesis.

Removal of DACH from HMDA

The removal of the DACH "impurity" from HMDA fractions is an important preliminary step in industrial polyamide synthesis in order to assure polymer homogeneity.[18] This is accomplished economically and efficiently by the preferential acid-catalyzed reaction of DACH in the presence of HMDA with a sugar such as sucrose, fructose and glucose to form products of low volatility from which the desired HMDA can be directly distilled.[18] HMDA with a reduced DACH impurity level can be prepared by this method using industrial molasses as a convenient

source of sucrose.[18] The residue from such treatment is not, however, a suitable source of purified DACH.

Separation of DACH Isomers

As shown in Table 2, most commercial DACH is a mixture of cis and trans isomers. Although pure trans-DACH is now available from Oxid, cis-DACH is not available at present. If pure DACH isomers are desired, it is necessary to separate them from DACH mixtures. Various separation schemes have been devised.

Downing et al. obtained trans-DACH by the fractional recrystallization of an isomeric mixture of hexahydroquinoxalines[21] according to a procedure first developed by A. I. Smith.[19] The reaction of a DACH mixture with benzil results in a diastereomeric mixture of 2,3-diphenylhexahydroquinoxalines (DPHHQ) ( 4 and 5 ). Less soluble trans-DPHHQ ( 5 ) precipitates from the reaction mixture and can be obtained pure by recrystallization from absolute ethanol. The acid hydrolysis of 5 regenerates trans-DACH which can be isolated as the free diamine after base work-up as shown in Figure 3. This method also results in a residue enriched in cis-DACH. However, the residue is not suitable for obtaining pure cis-DACH in reasonable yield.

Toftlund et al.[8] obtained pure cis-DACH from a mixture enriched in the cis isomer (90% cis) by selective precipitation of the sulfate (Fig. 4). Similarly, the dihydrochloride salt of cis-DACH has been reported by Langer and Whitney to precipitate selectively from ethanol to give cis-DACH in better than 90% purity.[22] However, the same authors report that pure trans-DACH dihydrochloride selectively precipitates if the solvent is changed to methanol. The monohydrochloride salt of trans-DACH, on the other hand, is less soluble in 95% ethanol than is

the monohydrochloride of cis-DACH (present work). These findings are summarized in Figure 5.

Figure 3

Separation of DACH Isomers via DPHHQ

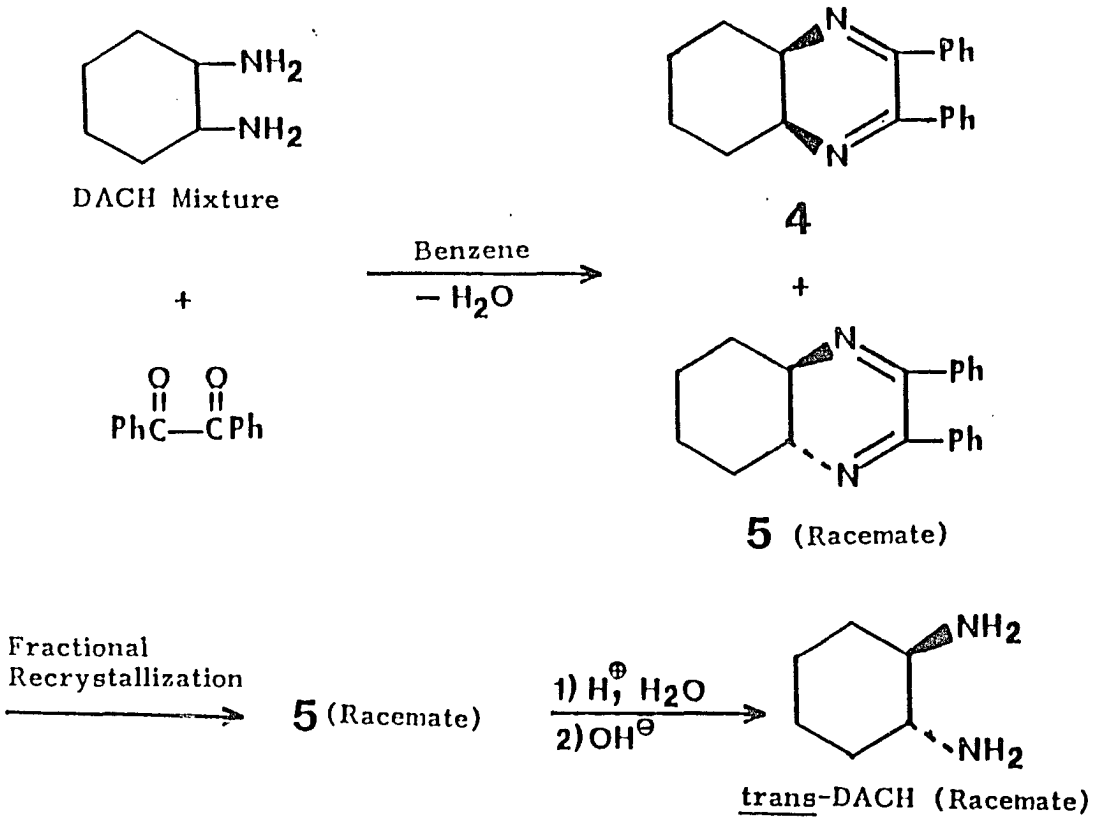



Figure 4

Separation of DACH Isomers via Sulfate Salts

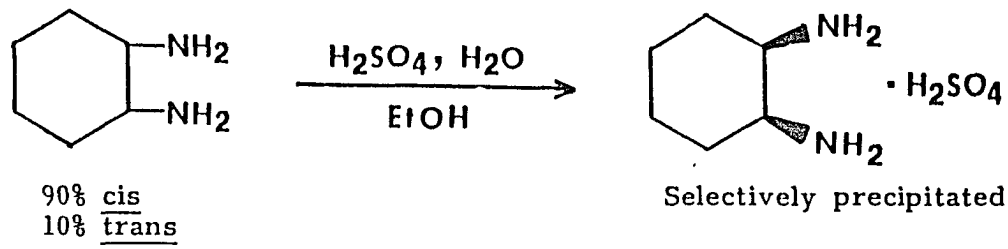
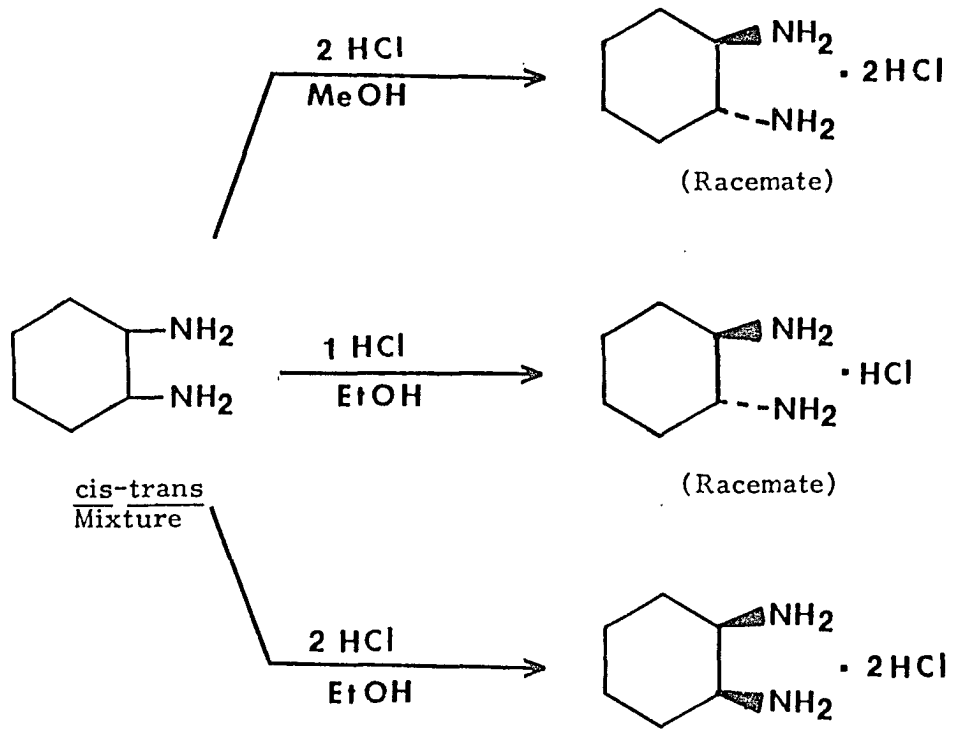


Figure 5

Separation of DACH Isomers via Hydrochloride Salts

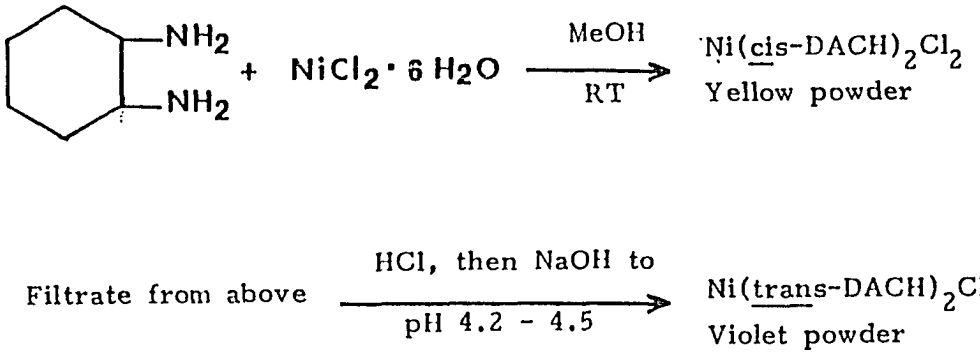



The procedure developed by Saito et al.[13,23] to separate cis and trans isomers of DACH via Ni complexes is, perhaps, the most convenient method, especially for preparation of a large quantity of cis-DACH (Fig. 6).

It has also been reported that DACH diastereomers can be separated by thin layer chromatography (TLC) on silica gel (ethanol: THF:$Et_2NH$:water = 6:3:1:1; $R_f$ = 0.58 for cis-DACH and 0.45 for trans-DACH).[13]

Figure 6

Separation of DACH Isomers via Ni Complexes




Tartaric acid resolution affords optically active trans-DACH, making this a special way of obtaining this isomer; tartrates of cis-DACH are considerably more soluble in water and are retained in the mother liquor along with one diastereomeric trans-DACH tartrate.

DACH Resolution

Trans-DACH was first resolved by Jaeger et al.[9,24] using (+)-(R,R)-tartaric acid, the isomer found more commonly in nature. Since then, a number of resolution procedures, all based on the formation of diastereomeric tartaric acid salts of DACH, have been reported.[12,17,25-29] Optically and chemically pure (-)-DACH is obtained by hydrolysis of the less soluble (R,R)-DACH·(R,R)-tartrate, recrystallized from water. Free diamine is recovered from aqueous base by continuous extraction with benzene[12,17,29] or by direct distillation of the organic phase that is separated from the basic aqueous phase.[27] The latter method is more convenient, and the time-consuming continuous extraction does not

substantially increase the final yield (present work). Sometimes, direct distillation of wet DACH does not give clean fractionation; distillation from NaOH is also not satisfactory, but distillation from benzene gives clean fractionation (present work).

It is important to use a high grade resolving agent, such as Aldrich Gold Label™ tartaric acid, in order to obtain pure white, well-formed salt after one recrystallization. Use of a lower grade acid gives brownish salt and may require repeated recrystallization to obtain the same result.

Jaeger and others added one more equivalent of (+)-tartaric acid and ethanol to the mother liquor left from resolution to precipitate (S,S)-DACH•2(R,R)-tartaric acid hydrate.[9,24-26,28] Treatment of this salt with base gave optically active (+)-DACH. The (+)-DACH was further purified by fractional recrystallization of its dihydrochloride salt, which was separated from racemic salt by hand![26] Because this method is inefficient, Langer et al. used slow crystallization of partially resolved (+)-DACH from a melt or from hydrocarbon solvent to increase its optical purity.[29]

Although "unnatural" (-)-(S,S)-tartaric acid is more expensive than "natural" (+)-acid, the mirror resolution using (-)-acid is the most convenient method of obtaining pure (+)-DACH.

Typical resolution procedures are given in the Experimental Section.

DACH Synthesis

There are a number of ways to synthesize DACH. Perhaps the most obvious would be the catalytic hydrogenation of o-phenylene-diamine, but the patent literature indicates that this reaction results in

a mixture of products and is therefore not a preferred synthetic method.[19,30-31] Other synthetic methods are summarized in Table 3.

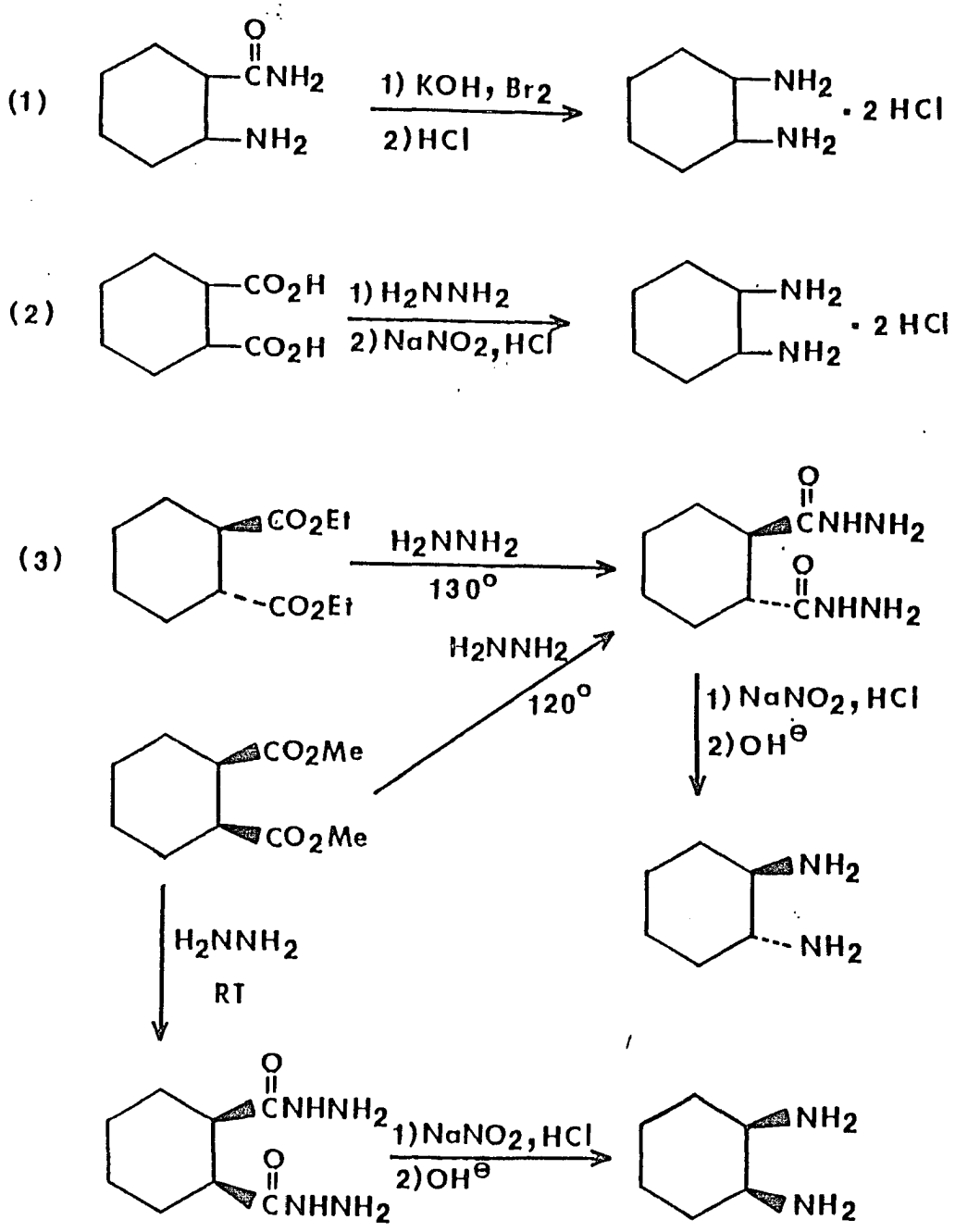
Einhorn and Bull[32] first synthesized DACH by the Hofmann rearrangement of hexahydroanthranilic acid amide (Entry 1). Neither the stereochemistry of the starting material nor that of the product is known, but the reported melting point of the bisbenzenesulfonamide of the product is consistent with that of the same derivative of trans-DACH reported later.[9,24]

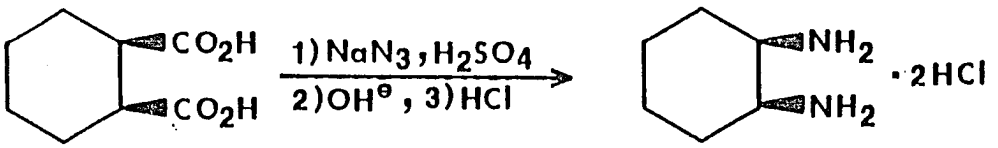
By the related Curtius rearrangement, Wieland et al.[33] prepared what might have been cis-DACH from 1,2-cyclohexanedicarboxylic acid of unknown configuration (Entry 2). This method was later applied by Yashunskii to obtain isomerically pure cis- and trans-DACH starting with cyclohexanedicarboxylates of known configuration.[14] It was found that a cis-dihydrazide intermediate (prepared from the cis-diester) would rearrange to the trans isomer at high temperatures (120 - 130°) to give a trans-DACH product. However, the preparation of a dihydrazide at room temperature from the cis-diester resulted in cis-DACH product (Entry 3). Similarly, the Schmidt rearrangement of cis-cyclohexanedicarboxylic acid gave cis-DACH (Entry 4).[34]

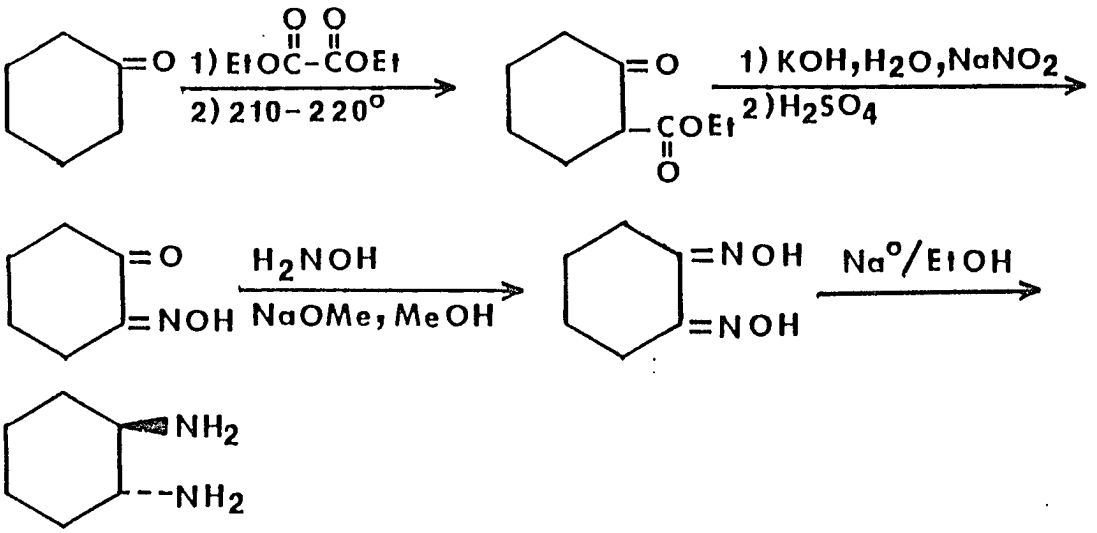
Jaeger et al. were first to report that the reduction of 1,2-cyclohexanedionedioxime with Na in abs. ethanol gave trans-DACH.[9,24] The configurational assignment was demonstrated by resolution of the product into two optically active antipodes (Entry 5). Others[34-36] also reported the preparation of trans-DACH by this method. It is not clear why the Na/EtOH reduction of the dioxime leads to the isolation of only one stereoisomeric product, but since the reported yields are relatively low (39 - 54%), it is idle to speculate on the true stereoselectivity of

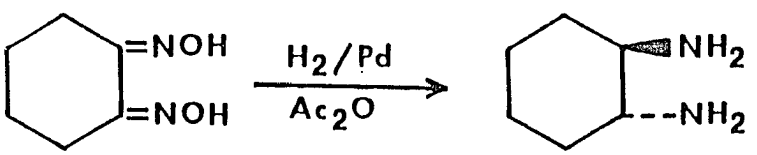
Table 3

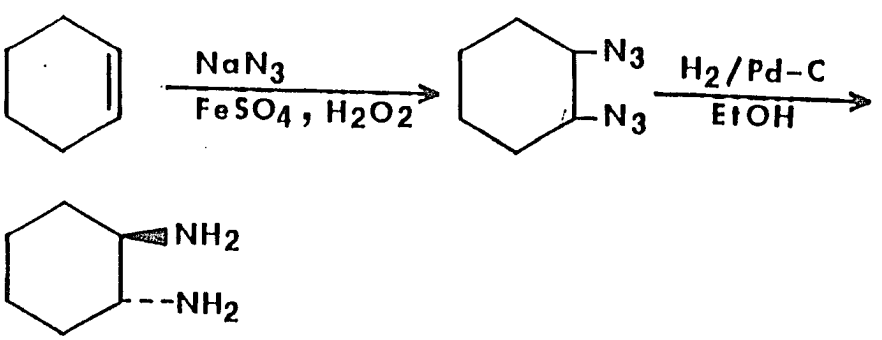
Methods of DACH Synthesis



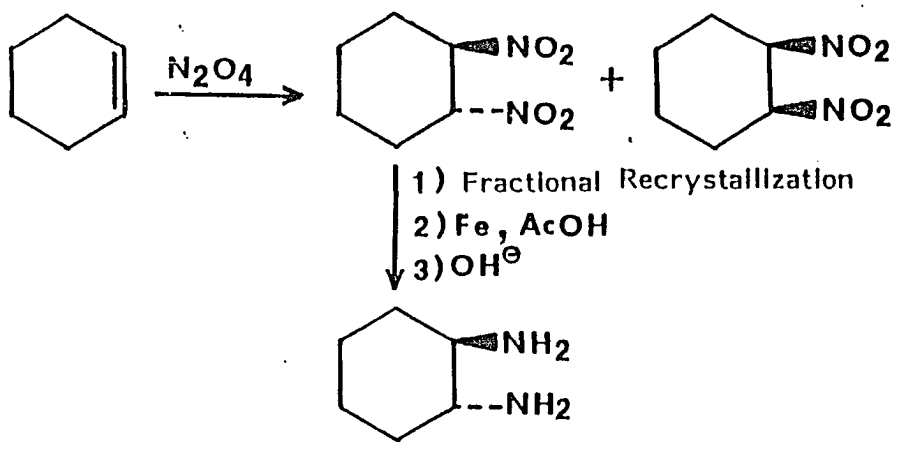
(4) 


(5) 

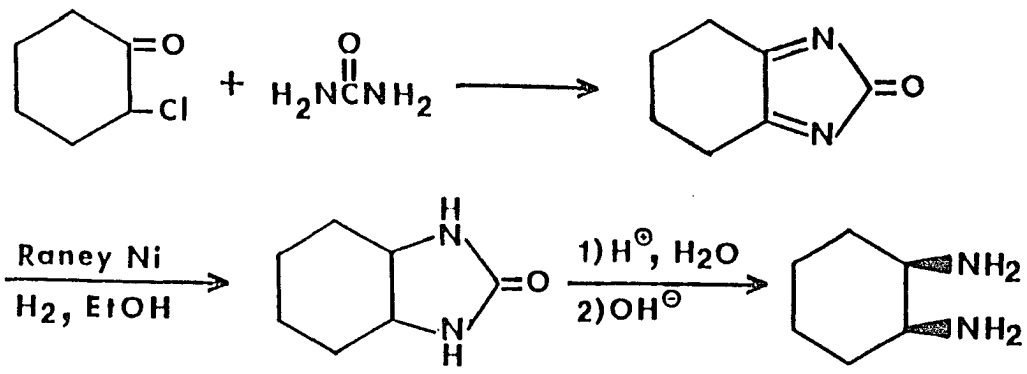

(6) 


(7) 

(8)




(9)




this reaction. Gullotti et al.[28] carried out a catalytic hydrogenation of the dioxime and obtained trans-DACH in 30% yield along with a mixture of several by-products (Entry 6).

The same workers synthesized trans-DACH by the catalytic hydrogenation of a diazide of unspecified configuration (Entry 7). The method developed by Minisci et al.[37] was used to prepare the inter-

mediate diazide from cyclohexene. The diazide is hazardous and the occurrence of a "terrible explosion" during its distillation was reported.[28]

Nielsen prepared dinitro compounds from cyclohexene using $N_2O_4$. He separated the diastereomeric dinitro intermediates, and from pure trans-dinitrocyclohexane trans-DACH was obtained by reduction with Fe in acetic acid. However, he was not able to isolate any pure cis-dinitrocyclohexane and was thus unable to prepare cis-DACH by this method (Entry 8).[10]

Simon reported a synthetic route to cis-DACH from 2-halocyclohexanone. Condensation with urea, hydrogenation of the resulting imidazolone, and hydrolysis of the imidazolidone thus produced yielded cis-DACH (Entry 9).[38]

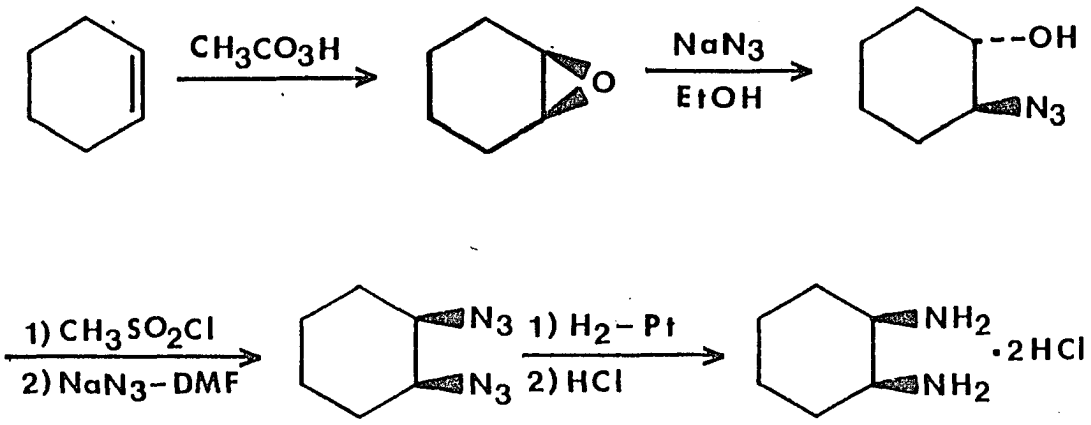
Swift and Swern[39] studied stereospecific syntheses of cis and trans-DACH (Fig. 7). Their synthesis of trans-DACH is based on the method first reported by Winternitz et al.[40] which involves the stereospecific trans ring opening of an aziridine with ammonia. Swift et al. improved the yield of trans-DACH by using azide ion rather than ammonia and subsequently reducing the aminoazide intermediate to diamine by hydrogenation. This route was the choice of later researchers to obtain trans-DACH.[41]

## General Uses of DACH

DACH is cited as a valuable intermediate for the production of dyestuffs, textile assistants, fungicides, pesticides and pharmaceuticals.[19] It is known to be a replacement for HMDA and ethylenediamine (EDA) in polyamide adhesives, petroleum chemicals, epoxides, and urethanes.[7] Lai prepared DACH derivatives for use as polymer

Figure 7

Synthesis of cis-DACH




Synthesis of trans-DACH

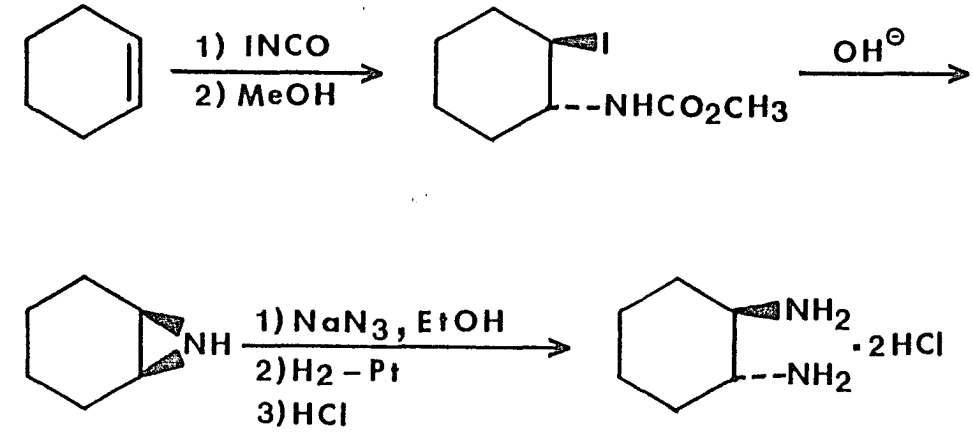
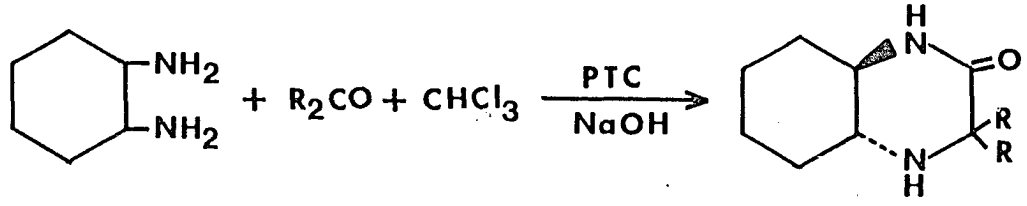



Figure 8

Hindered Amide



stabilizers[42] (Fig. 8).

In following sections, specific applications of DACH and DACH derivatives are discussed.

Stereochemistry of tris(DACH)-Transition Metal Complexes

The stereochemistry of tris(bidentate) complexes of transition metals has been studied extensively by CD, ORD, and X-ray methods.[3,43] EDA is perhaps the best known bidentate ligand used in these studies. EDA forms stable five-membered chelate rings in these octahedral complexes. The use of DACH as an EDA analog is also well-established.[43]

Jaeger and Bijkerk reported the preparations and optical properties of trans-DACH complexes of trivalent Co, Cr, and Rh ions in 1937.[9] In this early work, there was no discussion of the stereochemistry of these complexes in terms of their absolute configurations, although there was an awareness of the possibility of the formation of isomers.[25]

In the octahedral, tris(trans-DACH) complexes, there are eight possible stereoisomers. Two catoptric (enantiomeric) series, $\Delta$ and $\Lambda$, arise from the configurations around the metal ion. In the case of trans- DACH complexes, the conformations of the chelate rings formed by the ligand are fixed by the absolute configuration of the ligand: $\lambda$ for (-)-(R,R)-DACH and $\delta$ for (+)-(S,S)-DACH. For each of the catoptric series, there are four possible diastereomers, designated as $lel_3$, $lel_2ob$, $ob_2lel$, and $ob_3$.[25,44,45] These stereoisomers of trans-DACH complexes are shown in Table 4, where M is a metal center.

As can be seen in the table, only two possible stereoisomers can be formed for octahedral complexes starting with resolved DACH: $\Delta$-$lel_3$ and $\Lambda$-$ob_3$ for (-)-(R,R)-DACH and their enantiomers $\Lambda$-$lel_3$ and $\Delta$-$ob_3$ for (+)-(S,S)-DACH. Thus the use of pure DACH enantiomers, rather

Table 4

Four Enantiomeric Pairs of trans-DACH Complexes

| | | |
|---|---|---|
| 1. | $\Delta$-[M{(-)-(R,R)-DACH}$_3$-$\lambda\lambda\lambda$] | $\Delta$-lel$_3$ |
| | $\Lambda$-[M{(+)-(S,S)-DACH}$_3$-$\delta\delta\delta$] | $\Lambda$-lel$_3$ |
| 2. | $\Delta$-[M{(-)-(R,R)-DACH}$_2${(+)-(S,S)-DACH}-$\lambda\lambda\delta$] | $\Delta$-lel$_2$ob |
| | $\Lambda$-[M{(+)-(S,S)-DACH}$_2${(-)-(R,R)-DACH}-$\delta\delta\lambda$] | $\Lambda$-lel$_2$ob |
| 3. | $\Delta$-[M{(+)-(S,S)-DACH}$_2${(-)-(R,R)-DACH}-$\delta\delta\lambda$] | $\Delta$-ob$_2$lel |
| | $\Lambda$-[M{(-)-(R,R)-DACH}$_2${(+)-(S,S)-DACH}-$\lambda\lambda\delta$] | $\Lambda$-ob$_2$lel |
| 4. | $\Delta$-[M{(+)-(S,S)-DACH}$_3$-$\delta\delta\delta$] | $\Delta$-ob$_3$ |
| | $\Lambda$-[M{(-)-(R,R)-DACH}$_3$-$\lambda\lambda\lambda$] | $\Lambda$-ob$_3$ |

than the racemate, simplifies the stereochemical analyses of tris(DACH) complexes.

At first, the stereochemistry of diamine complexes was studied by CD and ORD methods to correlate the absolute configurations of complexes and of chiral ligands. In this way, the absolute configurations of trans-DACH enantiomers were first assigned.[3] More recently, stereochemical studies of complexes have been accomplished by X-ray crystallography. Thus in 1970, Marumo et al. confirmed the assignment of absolute configurations to the trans-DACH enantiomers by determining the structure of crystalline $(-)_{589}$-[Co{(+)-DACH}$_3$]Cl$_3$·5H$_2$O.[5] Since then the list of absolute configurational assignments for complexes of DACH and other ligands has grown with an increasing rate. The greater use of X-ray analysis has been made possible by

rapid improvements in both experimental and computational techniques.[43]

Today, the optical and X-ray methods complement each other, and the absolute configurations of transition metal complexes can be assigned with reasonable certainty on the basis of their CD spectra, which are obtained by simpler experimental means than data required for the X-ray method. A valid CD assignment, however, depends critically on the choice of appropriate reference complexes whose absolute configurations have been determined by the X-ray method and whose detailed CD spectra are also known.[43]

Two possible stereoisomers of the tris[(-)-(R,R)-DACH] complex of Co(III) were prepared and characterized by Piper and Karipides in 1964.[46] One of these isomers was reported by Jaeger and Bijkerk in 1937.[9] Analogous complexes of Rh(III), Ir(III), and Cr(III) are also known.[45] In 1976, Harnung et al. prepared and separated all eight stereoisomers of the Co(III)-tris(trans-DACH) complex and determined the relative equilibrium constants for the diastereomers.[45]

With cis-DACH, four stereoisomers of the Co(III) and Cr(III) complexes have been reported by Toftlund and Laier.[8] These isomers represent two enantiomeric pairs of stereoisomers arising from the spatial arrangement of two dissymmetric centers of the ligand and are named fac (facial) and mer (meridional). As in the case with tris-(trans-DACH) complex, each chelate ring may be one of two conformations, lel or ob, in theory, giving eight enantiomeric pairs of mer-isomers and four enantiomeric pairs of fac-isomers. However, the cyclohexane ring inversion at room temperature was found to be too rapid to allow the isolation of lel- and ob-conformers of fac and mer isomers.[8]

Square-Planar DACH Complexes

The use of bis(DACH) complexes of Ni(II) for the separation of cis and trans isomers of DACH from a commercial DACH mixture has already been described.[13,23]

DACH forms diimines (Schiff bases) when allowed to react with aldehydes and ketones such as salicylaldehyde and o-aminobenzaldehyde.[21] These diimines act as tetradentate ligands and they form square-planar complexes with Cu(II) ions. The optical properties of these complexes prepared from the trans-DACH enantiomer have been studied.[21]

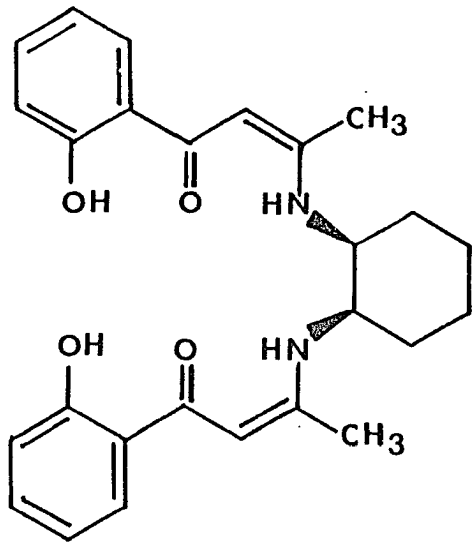
As an example of "compartmental" ligands, Bailey et al. prepared a derivative of cis-DACH, 6 with two different coordination sites[47] (Fig. 9). The dioxouranium (VI) cation has been found to occupy only the outer compartment and it retains a water molecule (solvent) in order to achieve seven-coordination. In contrast, the Cu(II) cation has been found to occupy the inner compartment. The X-ray crystallographic data have shown a marked tetrahedral twist away from the expected square-plane in the Cu(II) complex.[47]

The DACH diimine complex of Co(II) is an analog of Co(salen) (Fig. 10). Co(salen) and cobaloxime have been studied as a model for the coenzyme, Vitamin $B_{12}$.[48-49] Chiral Co(I) and Co(III) complexes of DACH diimine have been used in a kinetic resolution of propylene oxide[15,50-53] and in another kinetic resolution of an amino acid derivative.[54] The application of chiral DACH complexes will be discussed later.

Square-planar Pt complexes of DACH have been found to have high activity as anti-tumor agents.[55-57]

Figure 9

Compartmental Ligands

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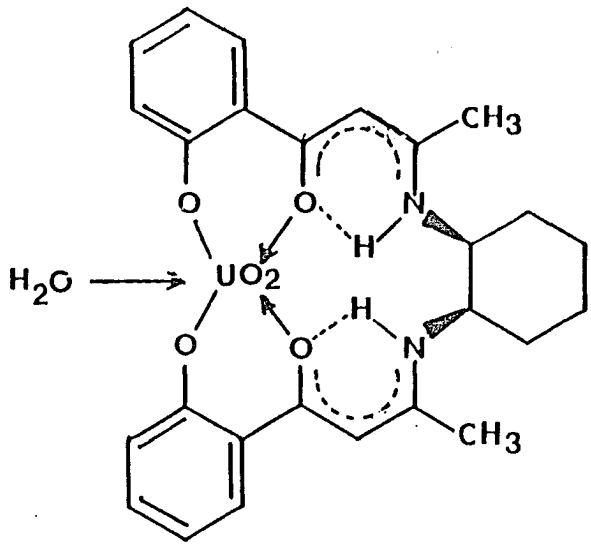


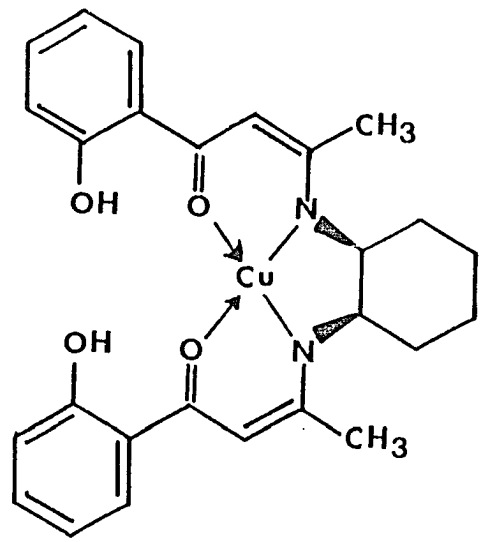
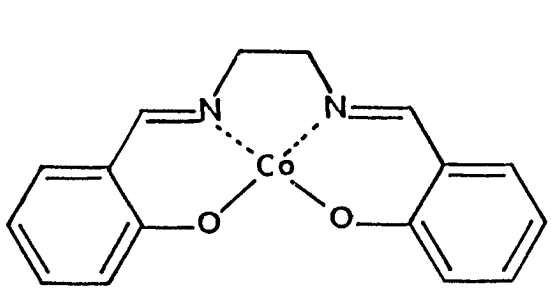
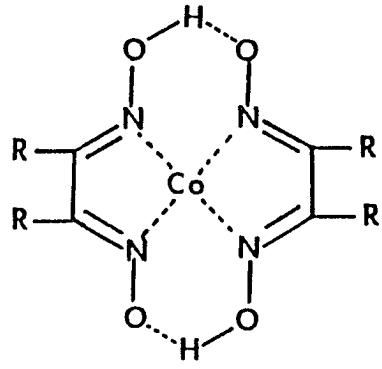



Figure 10

Vitamin $B_{12}$ Models




Co(salen)




Cobaloxime

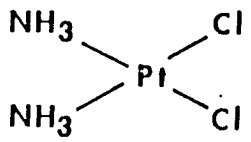
Anti-Tumor Pt(II) Complex

Rosenberg's discovery[58] of the anti-tumor activity of cis-dichloro-diammineplatinum(II) (DDP) in the late 1960's prompted the synthesis and pharmacological study of structurally related complexes. Of 52 organoplatinum compounds tested by Meischen et al., five were DACH-Pt complexes[55] ( 7 - 11 , Fig. 11). It was shown that DACH-Pt complexes were more effective than DDP against L1210 leukemia on an equimolar dose basis. Replacement of chloride with other anions increased the water-solubility (an important requirement for Phase I intravenous administration of potentially useful anti-tumor agents) and decreased the renal toxicity.[55]

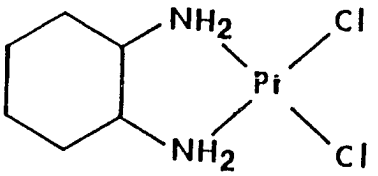
By August 1980, 1100 platinum compounds had been tested and 212 of them showed some anti-cancer activity.[59] DACH derivative ( 12 ) was found to be particularly promising as a substitute for highly toxic DDP in human cancer chemotherapy.[60]

Figure 11

Anti-Tumor DACH Complexes



DDP



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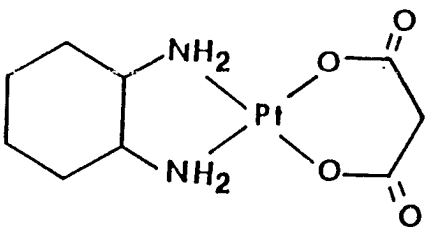

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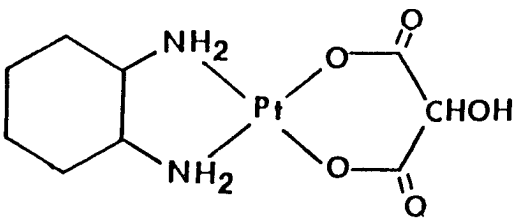

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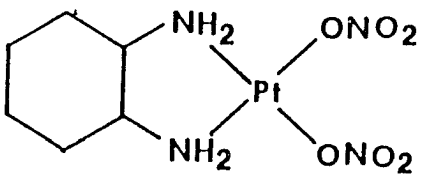

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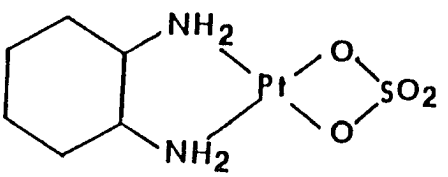

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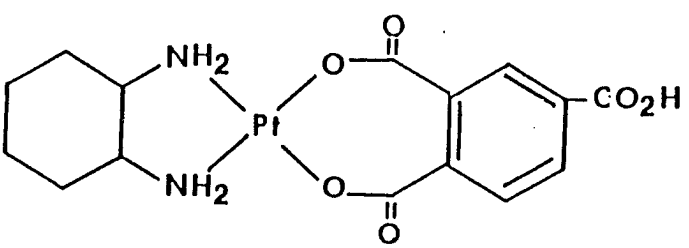
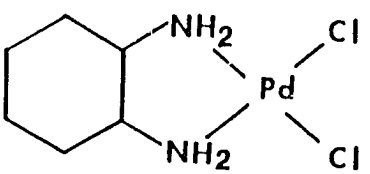


12



13

The stereochemistry of the DACH ligand is related to biological activity in these complexes. For compound 7, it has been found that a racemic trans-DACH ligand gives a complex that is more active than that of a complex prepared from cis-DACH. Furthermore, a complex prepared from (-)-(R,R)-DACH is more active than one prepared from (+)-(S,S)-trans-DACH.[61] Unfortunately, the stereochemistry of the DACH ligand is often not specified in the literature on Pt complexes. The National Cancer Institute found that some of the DACH used to prepare Pt complexes for clinical testing was not of high chemical and stereoisomeric purity.[62] The ability to prepare all of the stereoisomers of DACH in high chemical and isomeric purity is obviously important, and this author and co-workers have participated in a purchase order program to provide DACH-Pt compounds for NCI.

Rosenberg et al. have reported that whereas DDP is ineffective against certain animal colon cancers a palladium complex of DACH ( 13 ) is effective.[63]

DACH -Tetraacetic Acid

Ethylenediamine-N,N,N',N'-tetraacetic acid (EDTA) and its analog trans-1,2-diaminocyclohexane-N,N,N',N'-tetraacetic acid (trans-DACHTA) are known to chelate many metal ions.[27,64] With most metal ions, the complexes of trans-DACHTA are more stable than those of EDTA.[27] Because of this stability, trans-DACHTA is a useful complexing agent in analytical reactions.

For example, Carr and Swartzfager have described a complexometric titration for the determination of sodium ion in the presence of other alkali metal ions, alkaline earth metal ions, transition metal ions, and rare earth metal ions using trans-DACHTA as a chelating ligand.

The metal ions that form stronger complexes with trans-DACHTA than sodium are titrated first to a visual or potentiometric end point, then the sodium end point is determined using a sodium ion selective electrode.[65]

Hexadentate Co(III) complexes of trans-DACHTA are formed stereoselectively, giving only two of four theoretically possible isomers: $(+)_{546}$-[Co(-)-trans-DACHTA]$^{\ominus}$ and $(-)_{546}$-[Co(+)-trans-DACHTA]$^{\ominus}$.[27,66] This kind of stereoselective complexation is used to advantage in the spectropolarimetric titration of lead.[27] (-)-(R,R)-trans-DACHTA* (prepared from (-)-(R,R)-trans-DACH by reaction with $ClCH_2CO_2Na$) was used as a chelometric reagent. The optical rotation of the system was monitored during the titration and the large molar rotation of the complex gave a clear end point by graphical extrapolation.[27]

Lithium Chelates

Polyethylene polyamines form complexes selectively with inorganic salts of alkaline and alkaline earth metals. This is the basis for an important method of separating individual polyamines from multi-component samples.[67] Thus, a tris(β-dimethylaminoethyl)amine (iso-HMTT) impurity can be removed from N,N,N',N",N"',N"'-hexamethyl triethylenetetramine (n-HMTT) by selective complexation of iso-HMTT with LiBr in heptane. Otherwise, the separation of n-HMTT from iso-HMTT is extremely difficult. The facile separation of diastereomers of N,N,N',N'-tetramethyl-1,2-diaminocyclohexane (TMDACH)

---

* The direct resolution of racemic trans-DACHTA with (+)-phenylethylamine, (-)-quinine and (+)-cinchonine has been unsuccessful. The enantiomers of trans-DACHTA have been obtained by the decomposition of the cobalt(III) complex which has been resolved through the cis-dinitrobis(ethylenediamine)-cobalt(III) salt (Ref 66).

by an analogous method has been reported.[22,67] For example, a grossly impure diamine mixture (23% trans-TMDACH; 43% 1,3-TMDACH*; 31.7% cis-TMDACH; 1.7% unknown) gave a pure trans-TMDACH•LiBr complex when treated with 10 mole % LiBr.

In a competitive reaction, trans-TMDACH preferentially forms LiBr complex, but the LiBr complex of cis-TMDACH can be prepared by a stoichiometric reaction between cis-TMDACH and LiBr.[67] The complexation with $MgCl_2 \cdot 6H_2O$, on the other hand, shows the reversal of this selectivity and cis-TMDACH preferentially forms an insoluble $MgCl_2$ complex.[67]

N-Tetramethylated DACH and EDA form hydrocarbon-soluble complexes with $LiAlH_4$ and $NaBH_4$. These complexes have been reported to reduce many organic functional groups including aldehydes, ketones, esters, and acid anhydrides in aromatic hydrocarbon solvents such as benzene and toluene. The reduction is much faster and the yields are much higher than in the analogous reduction by $LiAlH_4$ alone in ether.[68,69] Asymmetric syntheses with $LiAlH_4$ and organolithium complexes of chiral trans-TMDACH will be described later.

DACH-Derived Anion Chelates

In previous sections, the complexation of cations (metal ions) by diamines has been described. Although the cation coordination chemistry is well-studied, the coordination chemistry of anions has received only limited study. In Lehn's study, a polyguanidinium derivative of trans-DACH is included as an example of anion complexing agent.[41] Compared to the stability of complexes of non-chelating

* N,N,N',N'-Tetramethyl-1,3-diaminocyclohexane

agents, the stability of complexes of chelating agents is often markedly increased. Such a phenomenon is called "chelate effect" and it is very large for cation coordination ($Ca^{2+}$-EDTA complex is $10^{10}$ times more stable than calcium acetate). Relative to complexation by diethylguanidinium ( 14 ), chelation of $PO_4^{3-}$ anion by polyguanidinium ions such as EDG, TREG and EDTEG (Fig. 12) has shown stability increases only on the order of $10^2$ to $10^3$. The stability increase in these reactions is attributed largely to an increase in electrostatic charge-charge interactions. Although the chelate effect for anion complexation was found to be very small, Lehn suggests that it may still have significant effects in biological systems on the anion transport across membranes and on the anion binding by receptor sites of biomacromolecules.[41]

Chiral DACH Derivatives

As already mentioned, both enantiomers of trans-DACH are readily available by the tartaric acid resolution. These isomers and their derivatives are useful as chiral modifiers for reagents used in asymmetric syntheses and as reference compounds for stereochemical correlations.

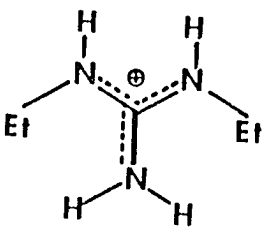
The dibenzoyl derivative of (R,R)-trans-DACH, ( 15 ) (Fig. 13) has been used as a reference in the CD study of amino acid conformation and in an extension of a chirality rule to the benzamide system.[70]

Osmate Ester Complex of TMDACH

The stereochemistry of glycols has been studied by proton nuclear magnetic resonance (NMR) spectroscopy using TMDACH as a chiral ligand in the formation of diastereomeric osmate(IV) esters[71] (Fig. 14).

Figure 12

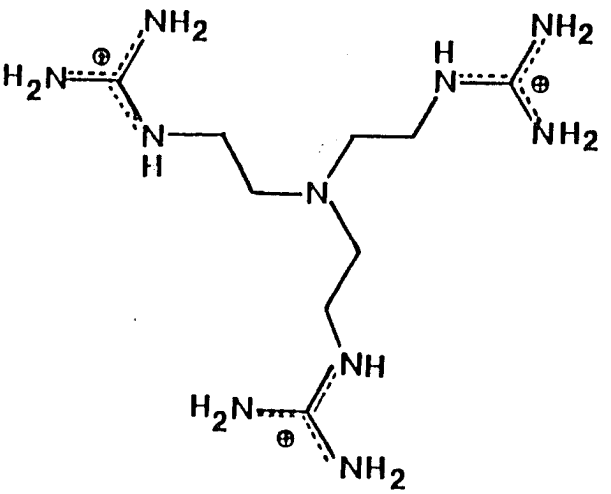
Polyguanidinium Ligands



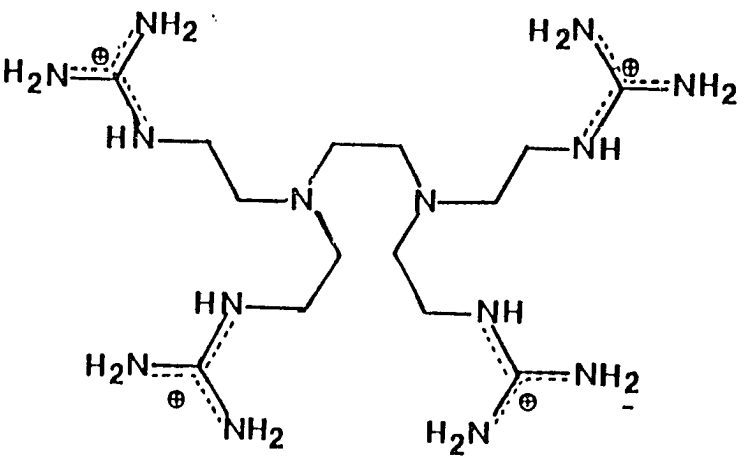
14



EDG



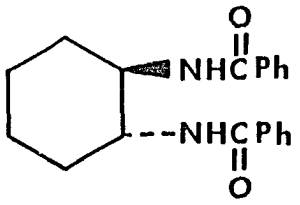
TREG



EDTEG

Figure 13

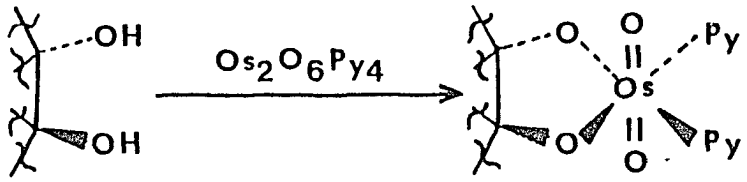
Dibenzoyl DACH Derivative

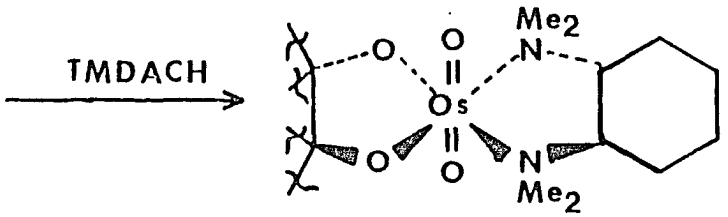



**15**

Figure 14

Osmate Ester Formation




For the (R,R)-2,3-butanediol osmate(IV) ester and (-)-(R,R)-TMDACH, two N-methyl signals were observed at $\delta$2.95 and 2.58 ppm.

The same ester treated with (+)-(S,S)-TMDACH, in contrast, had signals for diastereomeric N-methyl groups at $\delta$3.00 and 2.52. In the general case where the two chiral centers of a glycol are not chemical shift equivalent, all four N-methyl groups of TMDACH become chemical shift nonequivalent and give rise to four separate resonances. The reported chemical shift difference of diastereomeric complexes is very small ($\delta$0.00 - 0.04 ppm) but the authors found them useful in assigning the absolute configuration of an $\alpha$-isopropyl-$\alpha,\beta$- dihydroxybutyric acid fragment obtained by alkaline hydrolysis of pyrrolizidine alkaloid.[71]

## Asymmetric Reactions involving DACH

### Kinetic Resolution of Propylene Oxide

Propylene oxide is a useful chiral fragment for natural product synthesis.[72] Both enantiomers of propylene oxide can be prepared from naturally occuring (+)-lactic acid.[72,73] In the scheme shown in Figure 15, the optical purity of the epoxide product is dependent on the regioselectivity of the sulfonylation in the intermediate glycol. It has been established that the use of a hindered sulfonylating agent such as tripsyl chloride (Fig. 16) gives highly optically pure propylene oxide by assuring high sulfonylation regioselectivity.[74]

Kinetic resolution is another route for the preparation of chiral compounds. In the preparation of propylene oxide by a kinetic resolution procedure, the use of a chiral catalyst that incorporates DACH has been reported.[15,50-53]

The Co(salen) analog, N,N'-bis(salicylaldehyde)-(R,R)-1,2-trans-cyclohexanediiminatocobalt(II), ( 16 ), $[Co(II)(sal)_2\{(R,R)\text{-DACH}\}]$,

Figure 15

Propylene Oxide Synthesis

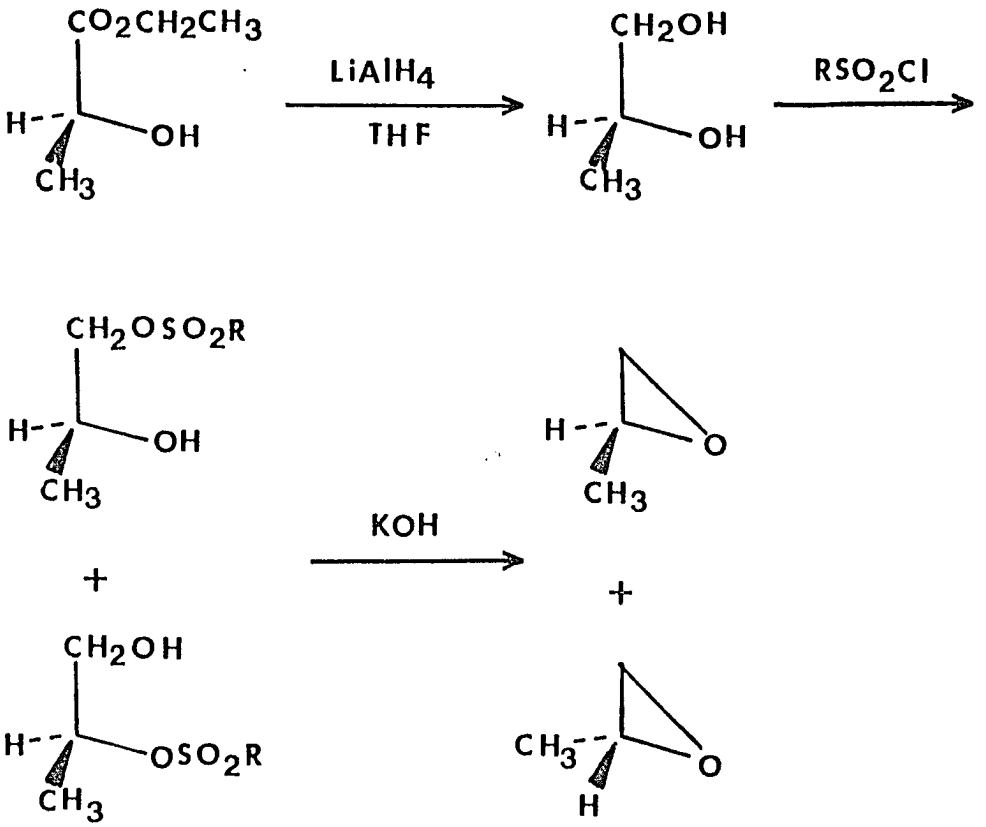
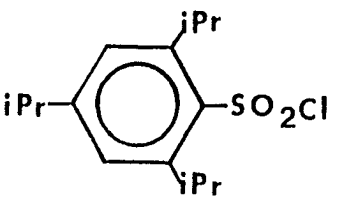



Figure 16

Hindered Sulfonylating Agent

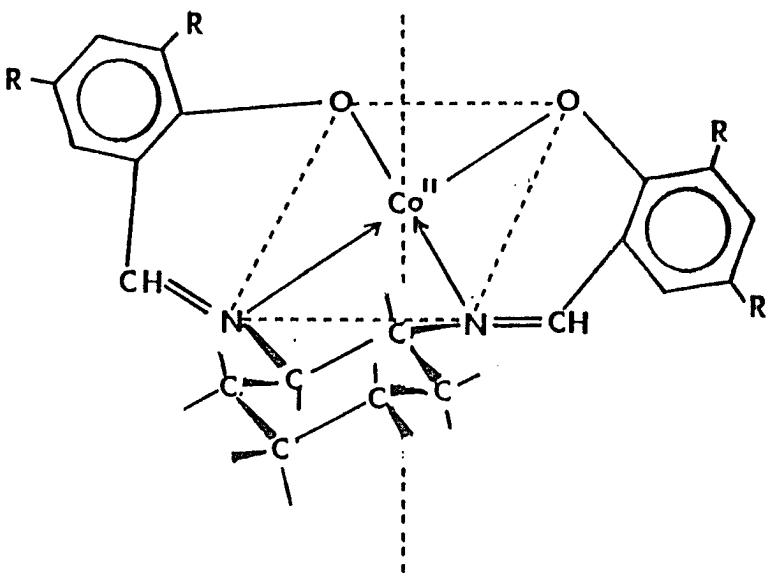



Tripsyl chloride

forms a Li [ Co(I)(sal)$_2$ {(R,R)-DACH}] salt on reduction with $LiAlH_4$ *in situ*. This chiral Co(I) complex preferentially reacts with (-)-(S)-propylene oxide with reported stereoselectivity up to 95%. However, this particular method is of little synthetic utility since the reported conversion is a mere 3% after 16 days.[15]

Figure 17

Chiral Catalysts for Kinetic Resolution




R = H **16**

Cl **17**

Of mainly theoretical interest is the fact that, in contrast, the Co(I) complex prepared by the reaction of 16 with BuLi reacts preferentially with (+)-(R)-propylene oxide.[50] Adding Lewis acid to the Co(II)-BuLi system affects the asymmetric selectivity so that the chiral catalyst preferentially reacts with (-)-(S)-propylene oxide. The authors suggest that alane, $AlH_3$, present in the reaction medium is acting as a Lewis acid and that the active Co(II)-$LiAlH_4$ system forms a

complex $Li[Co(I)(sal)_2\{(R,R)\text{-DACH}\}]\cdot AlH_3$.

More recently, the kinetic resolution of propylene chlorohydrin was carried out to yield optically active propylene oxide by base promoted cyclization in the presence of 16 and Co(III) complex prepared by the reaction of 16 with iodine.[52,53] The best asymmetric induction was observed for the cyclization of 1,3-dichloro-2-propanol catalyzed by the Co(II) complex 17, giving chloromethyloxirane of 60% enantiomeric excess (e.e.) in 53% yield. An analogous Ni(II) complex gave no asymmetric induction. The asymmetric induction is thought to occur by the action of an addition complex formed by the chiral catalyst and $K_2CO_3$ base. It was observed that $K_2CO_3$ is sparingly soluble in methylene chloride but becomes soluble in the presence of the metal complex.[53]

Although the optical and chemical yields of these reactions limit their synthetic utility, the thoroughness of the study allowed the formulation of an asymmetric cyclization mechanism. The proposed mechanism was based in part on physical data (CD spectra) for the asymmetric reagents. Often reaction mechanisms in asymmetric syntheses are based on presumed intermediates for which no direct physical evidence has been offered.

Stereospecific Complexation with Amino Acid

Some Co(II)-tetramine complexes, such as $Co(EDA)_2$, undergo stereoselective complexation with chiral amino acids. This stereoselectivity is higher with N-alkylated amino acids. The stereoselectivity of Co(II)-Schiff base complexes with a chiral amino acid is reported to be much higher than that of the corresponding tetramine complexes. Fujii et al. reasoned that in the Co(III)-Schiff base system, the N-alkylated amino

acid complexation might show quite high stereoselectivity.[54] It was found that the $\left[\text{Co(III)(sal)}_2\left\{\text{(S,S)(+)-}\underline{\text{trans}}\text{-DACH}\right\}\right]$ complex with N-benzyl-L-alanine exists as only one isomer when examined by proton NMR spectroscopy, indicating stereospecific complexation. Similar proton NMR examination of an N-benzyl-D-alanine complex, however, showed a 2:3 mixture of two diastereomers. Under air-oxidation conditions and in contact with a 2 mole equivalent of racemic N-benzylalanine, a Co-DACH-diimine complex was found to complex preferentially with N-benzyl-L-alanine. From the reaction medium, N-benzyl-D-alanine (93% e.e.) was recovered in 98% yield. After reduction with $NaBH_4$ and decomplexation, N-benzyl-L-alanine (94% e.e.) was obtained in 98% yield. With a large excess of racemic amino acid, the N-benzyl-L-alanine recovered from the complexation was nearly optically pure. The authors report that the N-benzylalanine showed no racemization under the experimental conditions and the Co-DACH diimine complex can be recycled repeatedly.[54]

Stereoselective Association of Complex Cation and Anion

Another application of optically active metal complexes as resolving agents is found in the stereoselective association between cationic metal complexes and anionic metal complexes. This stereoselectivity has been measured by ion-exchange chromatography.[75] The relative retention volumes of complex anion enantiomers on an IEX 220 anion-exchange resin when eluted by a solution of optically active cationic metal complex provided the required data. Of three cationic complexes studied, $\Delta$-$\left[\text{Co(III)}-\left\{\text{(R,R)-DACH}\right\}_3\right]$ ion gave the largest differences in the retention volumes of four anionic Co complexes. The authors discussed the mechanisms of chiral recognition, but it is not clear if this is a practical resolution method. In the case where an optically active complex cation is adsorbed

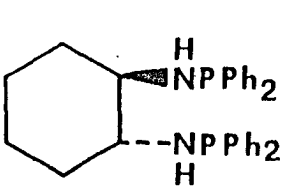
on the SP-Sephadex C-25 cation-exchanger and the racemic anion complex is eluted with water, the degree of resolution of anions is reported to be very small and the chirality of the resin matrix itself without chiral cationic complex gave some resolution of anions.[75]

Asymmetric Hydrogenation

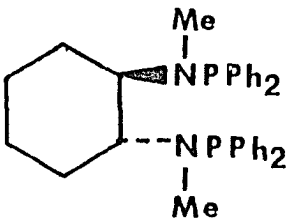
The asymmetric catalytic hydrogenation of olefins is now an efficient method of obtaining amino acids with high optical purity.[76,77] Some of the most effective catalysts are soluble phosphine-rhodium complexes. Such chiral catalysts prepared from trans-DACH enantiomers and their derivatives have been reported to give excellent asymmetric induction in the hydrogenation of N-acylaminocinnamic acids.[78-82] Bis-aminophosphine-Rh complexes prepared with ligands such as 18 and 19 have shown remarkable stereoselection. Although the two ligands have the same (R,R)-configuration, they induce the synthesis of enantiomers. This reversal of product configuration when N-methyl groups are introduced has been attributed to a change in the helical orientation of phenyl groups in the Rh complex (from left-handed to right-handed helical arrangement) by the increased steric demand of the N-methyl groups. This argument is supported by an X-ray structural determination of the Rh complex and by a study of the CD spectra of the catalysts and ligands in solution.[83] The degree of asymmetric induction by 19 is much higher (89-92% e.e.) than 18 and it is dependent on the substrate structure and on the solvent. These observations have been incorporated into a proposed mechanism of chiral recognition. With 18, amino acids of 41-43% e.e. were obtained. Kleemann et al. applied the same catalytic system to dipeptide precursors to obtain similar asymmetric induction (38-39% e.e.).[84]

Figure 18

Bis-Aminophosphine Ligands




18




19

Asymmetric Synthesis with Lithium Chelates

Optically active N-permethylated DACH, (-)-TMDACH or (+)-TMDACH, (prepared from resolved DACH by the Eschweiler-Clarke procedure) form optically active lithium chelates. The TMDACH complex of $LiAlH_4$ and $LiBH_4$ are soluble in hydrocarbon solvents and they are chiral reducing agents for organic substrates. In particular, the (-)-TMDACH•$LiAlH_4$ reagent gives a modest asymmetric induction when used to reduce unsymmet-rical ketones (up to 30% e.e., generally about 10% e.e. or less).[85,86]

Organolithium reagents complexed with (-)-TMDACH add alkyl and aryl groups to aldehydes asymmetrically (less than 10% e.e.).[85,86] When optically active trimethyl DACH (TriMDACH) is used instead of TMDACH, optically active lithium salt is formed. This lithium amide can complex with aluminum hydride and borohydride moieties to provide new chiral reducing agents. The degree and the direction of asymmetric induction by these new reagents are quite different from those of the related TMDACH complex reagents (Table 5).[87]

Table 5

Asymmetric Synthesis with Lithium Chelates

| Reagent | Substrate | Product | |
|---|---|---|---|
| (R,R)-TMDACH + $LiAlH_4$ | $Ph-\overset{\overset{O}{\|}}{C}-CH_3$ | $Ph-\overset{\overset{OH}{\|}}{\underset{\underset{H}{\|}}{C}}-CH_3$ | 7% e.e. (+) |
| (R,R)-TriMDACH + $LiAlH_4$ | " | " | 33% e.e. (+) |
| (R,R)-TMDACH + BuLi | $Ph-\overset{\overset{O}{\|}}{C}-H$ | $Ph-\overset{\overset{OH}{\|}}{\underset{\underset{H}{\|}}{C}}-C_4H_9$ | 9% e.e. (-) |
| (R,R)-TriMDACH + 2 BuLi | " | " | 10% e.e. (+) |

Potential Applications

In the survey of properties and applications of DACH and its derivatives above, some examples of asymmetric synthesis using DACH-derived reagents are given. Chiral DACH and its derivatives are potential catalysts for asymmetric Michael additions and aldol condensations. Modification of amino groups provides the DACH ligand as a secondary or tertiary diamine, or even as a quaternary ammonium salt suitable as a potential chiral phase-transfer catalyst. Like TriMDACH, two amino groups need not be the same. One amino group can be a primary or secondary amine which reacts with organolithium or metal hydride reagents while the second group can be a tertiary amine which takes part in the chelation of metal ions. Synthesis of DACH derivatives with chiral nitrogen atoms is also possible. For example, dibenzylation of known N,N'-dimethyl-(R,R)-trans-DACH (trans-DMDACH) leads to a new diamine with two new chiral centers at nitrogen atoms. It will be interesting to see what asymmetric induction can be observed by the reactions of the lithium chelates of such a ligand. Many chiral transition metal complexes of DACH derivatives are well-characterized but very few have been used in asymmetric synthesis. Transition metal complexes of DACH dioxime and diimine are potential catalysts for asymmetric synthesis mediated by organometallics.[88]

In the present study, chiral diamines were prepared from DACH and were used to modify metal hydride reagents. Asymmetric reduction by these new reagents was examined.

## II: DACH ANALYSIS

The chemical purity and the cis/trans isomer ratio of commercial DACH can vary widely. Poor sample quality or a high percentage of cis isomer can adversely affect DACH resolutions. In the present work, it was deemed important to know the chemical purity and the isomer ratio of DACH samples used for resolution studies and derivatization. The methods for DACH analysis reported in the literature include the use of gas chromatography (GC) to detect DACH and its tetramethyl derivative, and also the use of proton NMR spectroscopy.

### Direct GC Analysis of DACH

Primary aliphatic amines and diamines are difficult to analyze by GC since these strongly polar compounds interact with the column to give an undesirable adsorption effect.[89] Treatment of the column with KOH deactivates it and eliminates "tailing" of the peak thus facilitating quantitative peak calculations.[89,90]

Many commercial samples of DACH are contaminated with HMDA which cannot be removed easily by fractional distillation.[18] However, Smith et al. reported that a mixture of cis/trans-DACH and HMDA can be separated on an 8-meter column containing 10% DC 710 and 5% KOH on Chromosorb W.[90] Yet, even under conditions where the retention time was over 30 minutes, base line separation of peaks was not obtained. An Apiezon L KOH-doped column was reported to give a partial separation of DACH isomers, but Carbowax 20M with KOH was reported to give only the separation of DACH and HMDA; no separation

of DACH isomers was observed.[90]

In the present study, it was discovered that the analyses of DACH samples reported by commercial suppliers were often incorrect. It was found that this was, in one instance, caused by the choice of an inappropriate GC column. In the case of Aldrich Chemical, its reportedly 98% pure DACH sample (cis/trans ratio reported to be 13:87) was found to be only 85% pure, and the cis/trans ratio was found to be 45:55 by our method of analysis. The column used by the Aldrich quality control group separated DACH and HMDA and a small amount of an unidentified third component, but they had misinterpreted peaks actually representing the HMDA:DACH ratio as the cis/trans ratio of DACH isomers and had also misassigned the third peak to HMDA. Other investigators have also noted the frequent use of erroneous analytical data for DACH by its suppliers.[62]

Lai reported the GC analysis of DACH using a combination of two 6-ft columns, one coated with Apiezon L and the other with Ucon, both deactivated with KOH. Unfortunately, it is difficult to assess from Lai's paper and subsequent private communications whether this system actually separated the DACH diastereomers.

Oxid is a supplier of an exceptionally pure trans-DACH. This company analyzes DACH on a capillary column packed with a nonpolar stationary phase. The detail of their analytical method is given in Appendix A. Because of the lack of a suitable instrument to carry out this type of chromatographic analysis, Oxid's method was not examined as part of the present study.

A capillary instrument must be readily available in order routinely to analyze DACH by GC. Even with such instrumentation, the efficacy

of the column must be proven, because the results of direct GC analysis can be easily misinterpreted.

GC Analysis of TMDACH

Tertiary aliphatic amines and aromatic amines are not as difficult to analyze by GC as primary or secondary amines. The diastereomers of N-methylated DACH (TMDACH) can be separated on a Carbowax 20M + KOH column.[12,22,67] The same column cannot be used to analyze unmethylated DACH sample since the components trail badly. It has been noted that "a sample containing 60% trans-DACH plus four other components gave one beautifully symmetric VPC peak before methylation"![62]

TMDACH is prepared from DACH by the Eschweiler-Clarke procedure[22,91] or by four successive lithiation steps with butyl lithium followed each time by alkylation with methyl iodide.[22]

There is always a danger of introducing new factors into the analysis, if the composition of the mixture is determined after carrying out a reaction. One can be assured of the accuracy of the analysis only if the conversion is quantitative for all the components present in the original mixture. Otherwise, the composition of the derivatives may not reflect the original composition accurately. Incomplete conversion may lead to many reaction components and thus the chromatogram will contain extra peaks. In cases where the column inadequately separates the components present in the original mixture, incomplete conversion will lead to further difficulty in the interpretation of the resulting chromatogram. The calibration may be especially difficult in such a case, if it can be done at all.

N-Methylation of amines by the Eschweiler-Clarke procedure

normally calls for the reaction mixture to be refluxed at the most for overnight but often for shorter period.[91,92] It was found in this study that this kind of reaction time is inadequate for the N-tetramethylation of cis-DACH. In fact, it was found that at least a seven-day reaction time is required to convert cis-DACH to its tetramethyl derivative under the usual Eschweiler-Clarke reaction conditions. Under the reaction conditions of about 100°C for a prolonged time, HMDA decomposed to a significant extent even under a nitrogen atmosphere. A detailed discussion of the Eschweiler-Clarke N-methylation of DACH appears in Section III. In agreement with the present study, a group at Exxon Research has also found that the N-tetramethylation of DACH mixture goes very slowly. The Eschweiler-Clarke procedure was, therefore, modified by allowing the reaction mixture to reflux for 36-48 hours with fresh portions of formaldehyde being added approximately every 10 hours.[22]

The uncertainty of complete conversion of DACH to tetramethyl derivatives within the reaction period and the decomposition of more fragile components in the mixture by the prolonged exposure to a high temperature are disadvantages of the methylation as an analytical method. In addition, GC analysis of DACH via tetramethyl derivatives requires a substantial investment of time to prepare the derivative and is not at all conducive to a quick routine analysis of DACH samples. Therefore, an alternative method for a direct analysis of DACH samples was sought.

Proton NMR Analysis

Proton NMR spectroscopy is used in many routine analyses in organic chemistry. The importance of this method is reflected in the

inclusion of this topic early in introductory texts for the undergraduate organic chemistry course. Proton NMR spectroscopy is also an important method for the quantitative analysis of mixtures of organic compounds, provided such mixtures have at least one set of suitable proton signals for each component present. The integrated area (signal size) of proton peaks is proportional to the number of the equivalent proton nuclei present in the sample.

Toflund et al. reported that the cis/trans isomer ratio of DACH can be determined from a proton NMR spectrum. The spectrum of cis-DACH is reported to show two rather broad peaks at $\delta$1.45 and 2.80 ppm, whereas that of trans-DACH shows three multiplets around $\delta$1.20, 1.70, and 2.35. The peaks at $\delta$2.80 and 2.35 were assigned to the methine protons and it was reported that these nonoverlapping peaks can be used to measure the relative amounts of cis and trans-DACH in a mixture with accuracy.[8]

As can be seen in Fig. 19, 20, and 21, the proton spectra obtained in this study are not amenable to the quantitative analysis of DACH isomers. The three multiplets described by Toftlund et al. for trans-DACH are better described as one extremely broad peak ($\delta$0.60-2.50) with three recognizable humps at $\delta$1.2, 1.7, and 2.25 (Figs. 20 and 21). At 100 MHz, the peaks are better defined, but the methine peak still is not resolved from the methylene peaks. The most prominent feature of these spectra is the sharp amine peak near $\delta$1.3 ppm for DACH dissolved in $CDCl_3$ and $CCl_4$. The chemical shift of this peak is highly dependent on the solvent and on the concentration. It is exchanged with deuterium upon addition of $D_2O$ (Fig. 21) and thus is absent in the spectra of DACH dissolved in $D_2O$ (Figs. 22-23). The

Figure 19

cis-DACH in $CDCl_3$

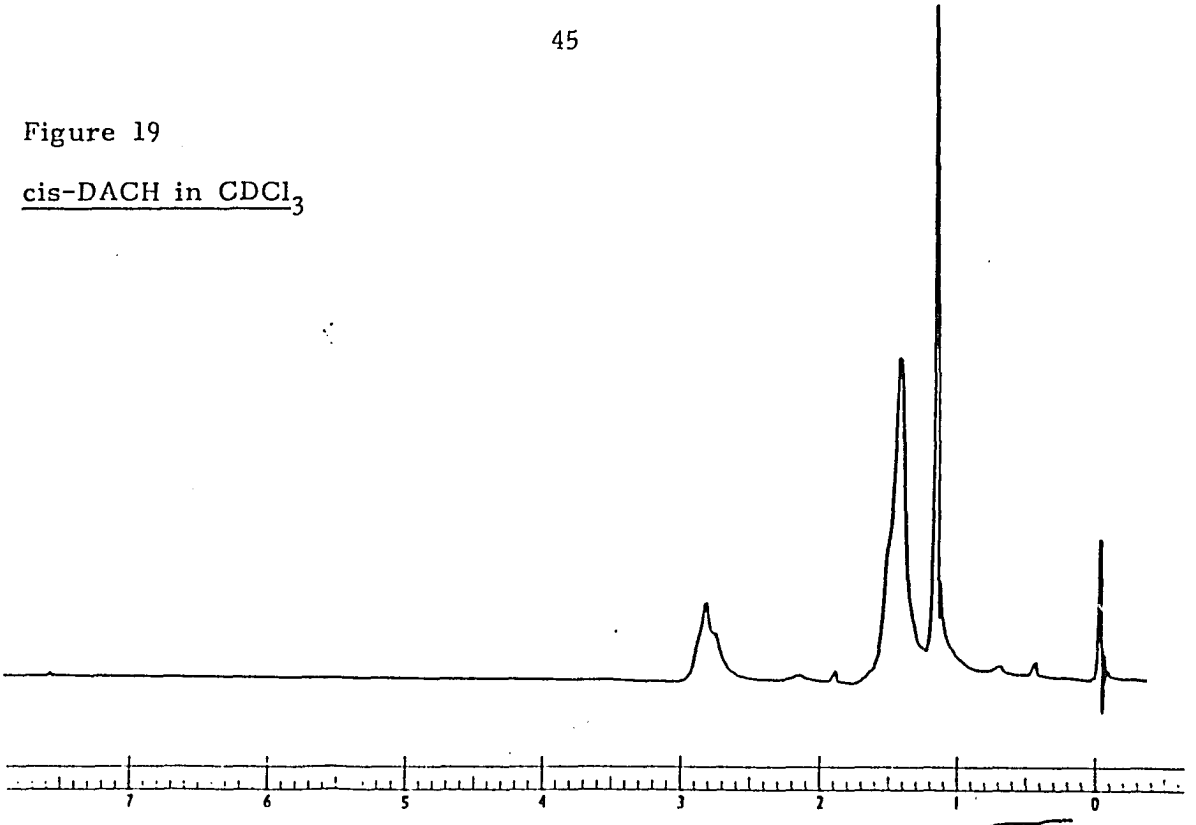



Figure 20

(+)-DACH in $CDCl_3$

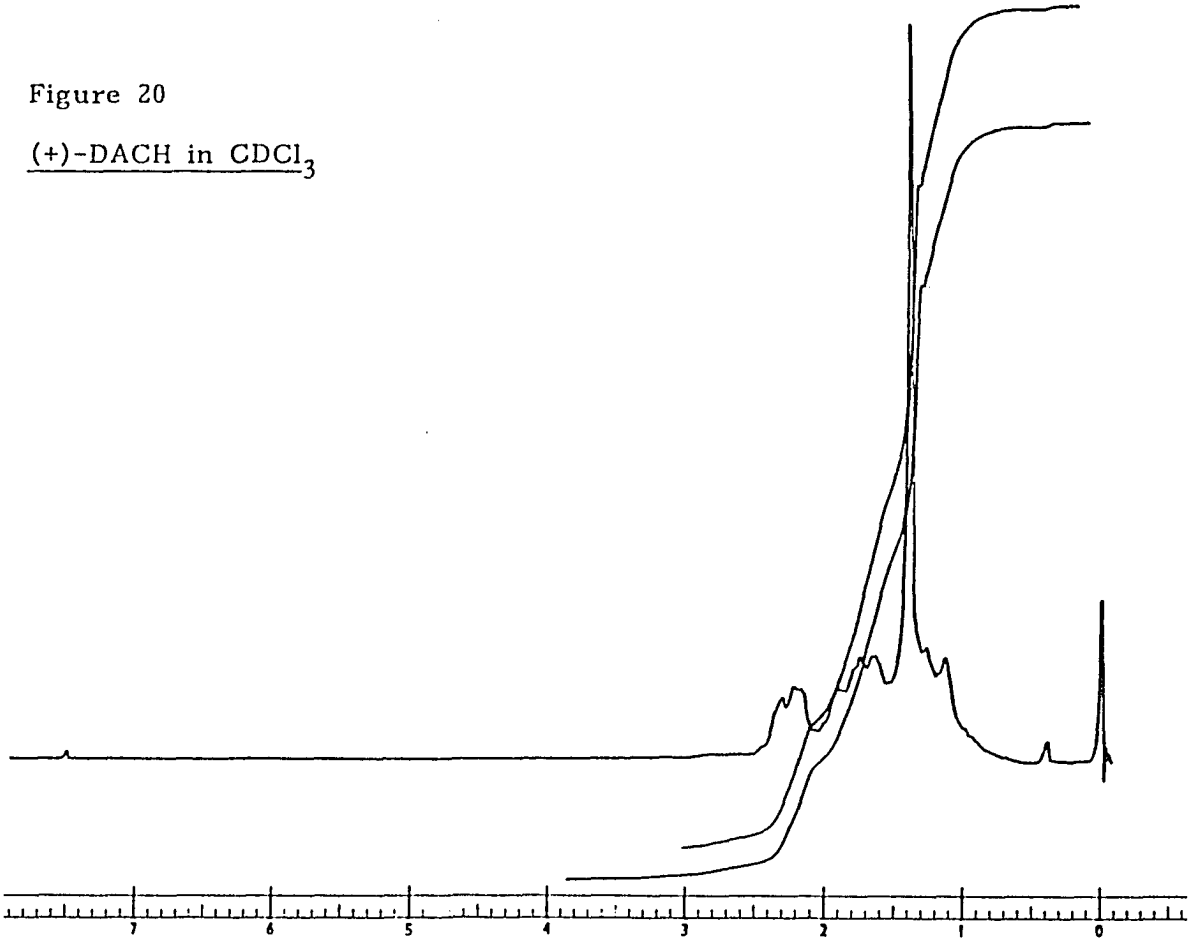
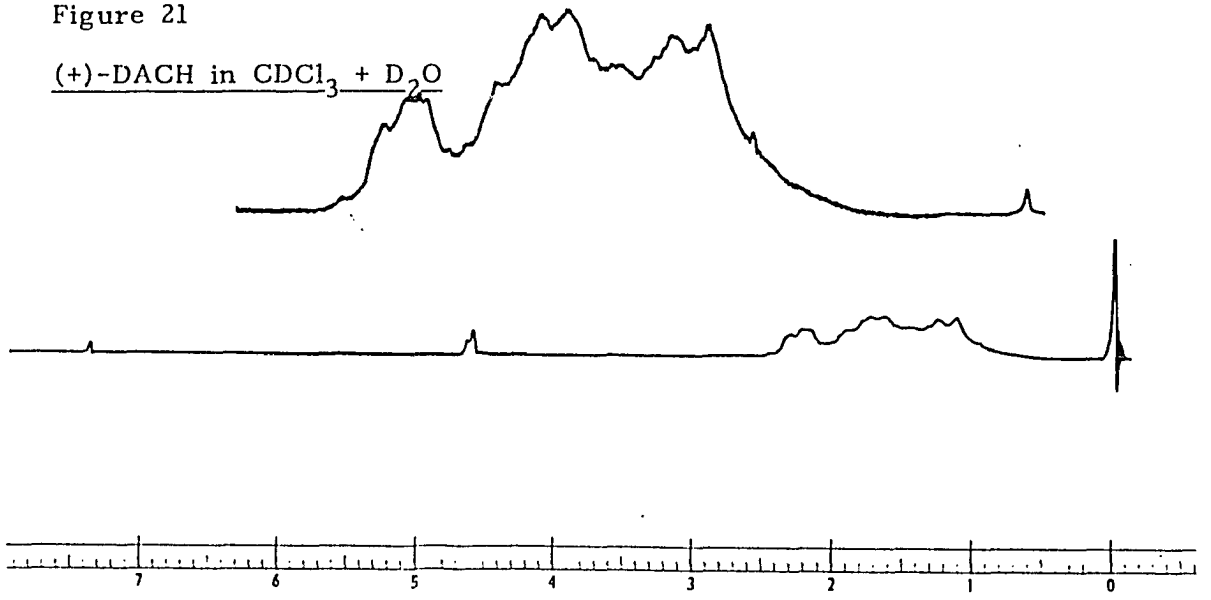


Figure 21

(+)-DACH in $CDCl_3$ + $D_2O$




multiplets are observable in the spectrum of trans-DACH at high concentration (Fig. 23), but the methine peak is centered at $\delta$2.25, instead of 2.35, and still overlaps with the methylene peaks. It is difficult to understand how such a peak can be used for an "accurate" analysis.

For the cis isomer, a downfield peak at $\delta$2.60-2.85 that does not overlap with other DACH peaks was observed. Therefore, it is possible to check for the presence of cis-DACH in a pure DACH sample by proton NMR (Fig. 24). However, this is not possible if a sample contains HMDA, since it, too, has a downfield peak at $\delta$2.30-2.85 (Fig. 25). It is clear from the spectra of DACH mixtures containing HMDA (e.g., Fig. 26) that the composition cannot be determined accurately by proton NMR; it is not even possible to obtain crude estimates using 60 MHz spectrometer.

Sudmeier et al. studied the conformation of DACH and its derivatives using proton NMR spectroscopy.[93] They found that the chemical

Figure 22

cis-DACH in $D_2O$

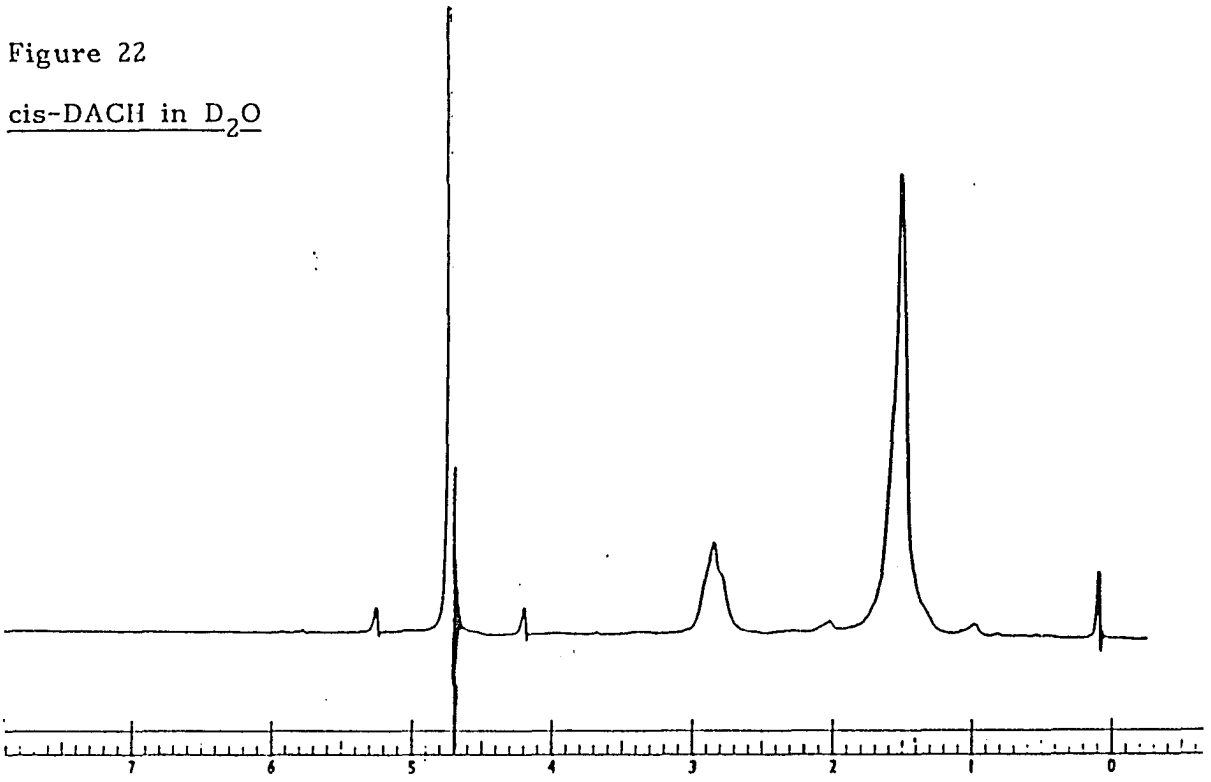



Figure 23

trans-DACH in $D_2O$

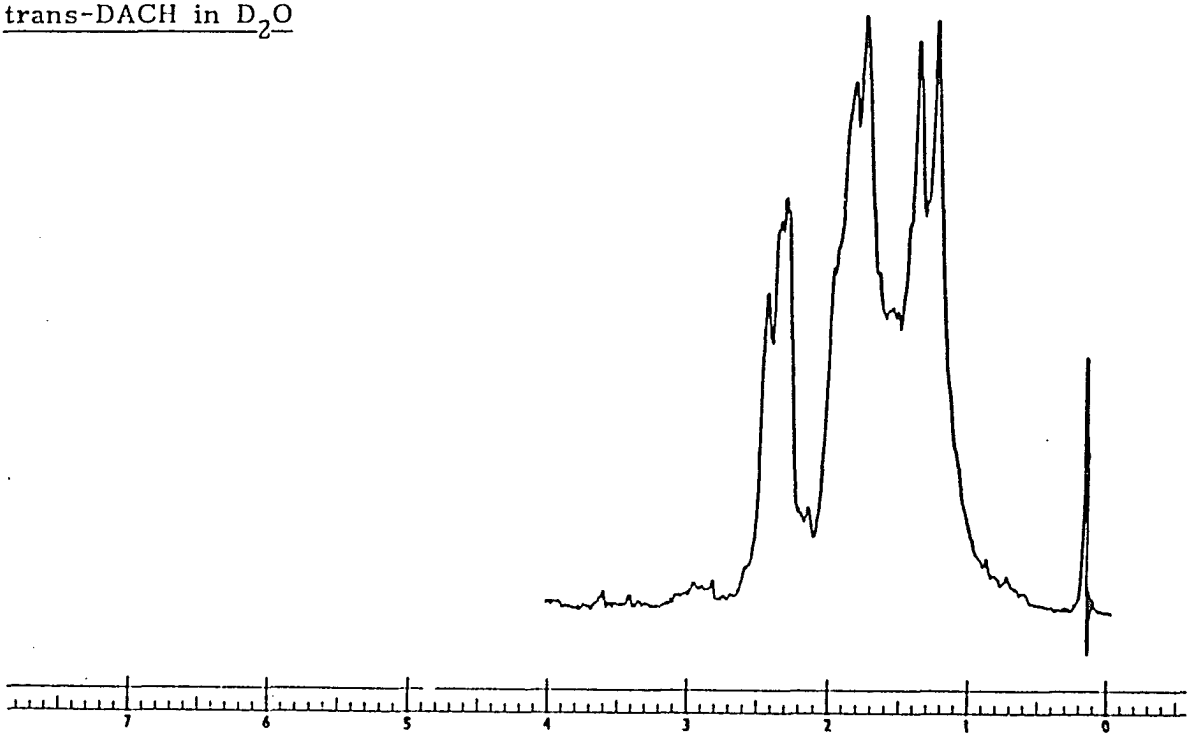


Figure 24

98% Pure DACH (cis-trans Mixture)

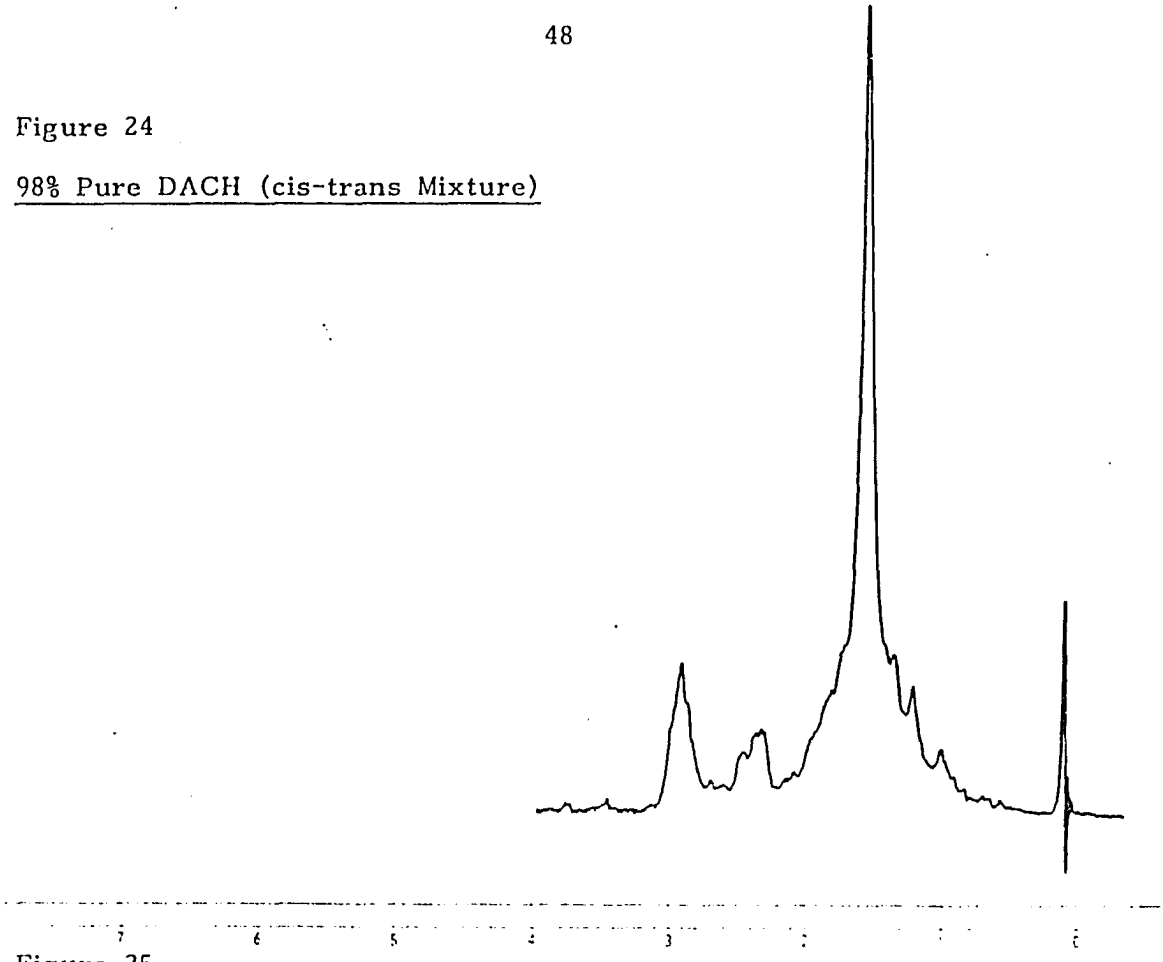


Figure 25

HMDA in $D_2O$

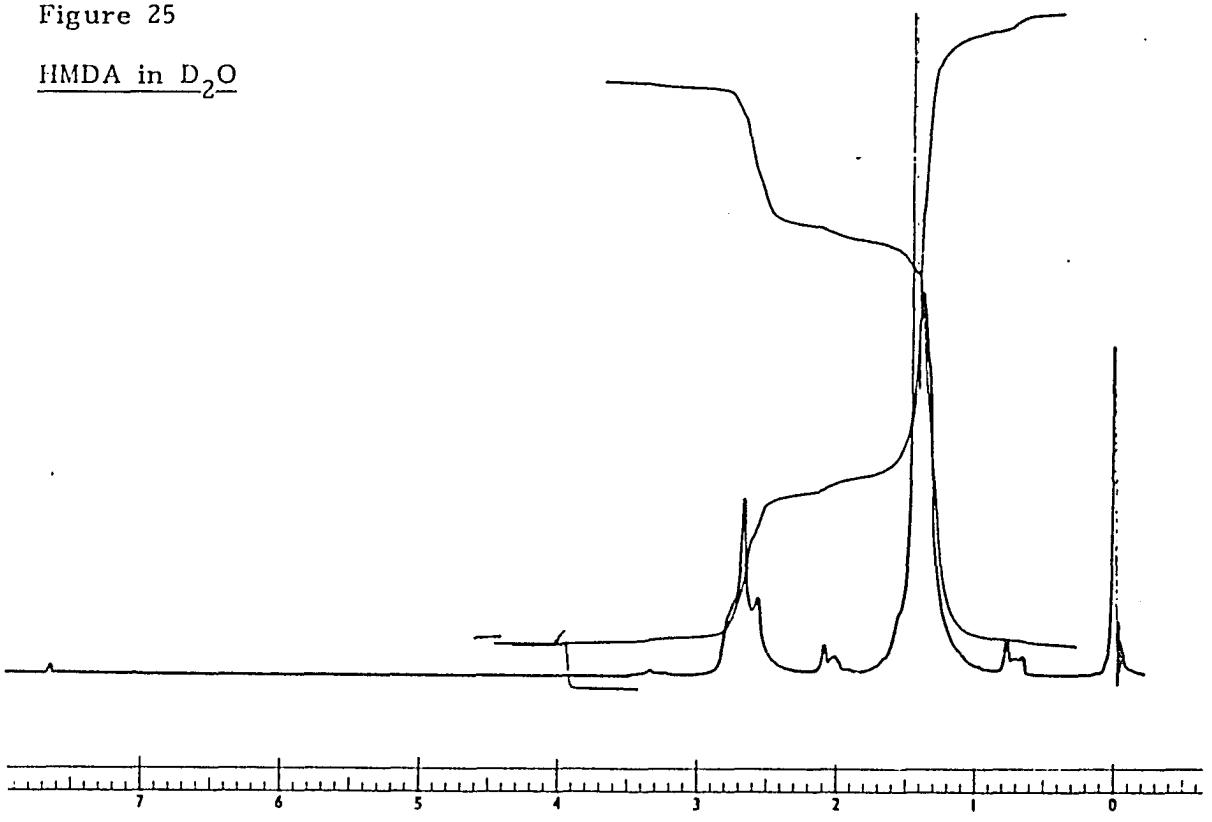
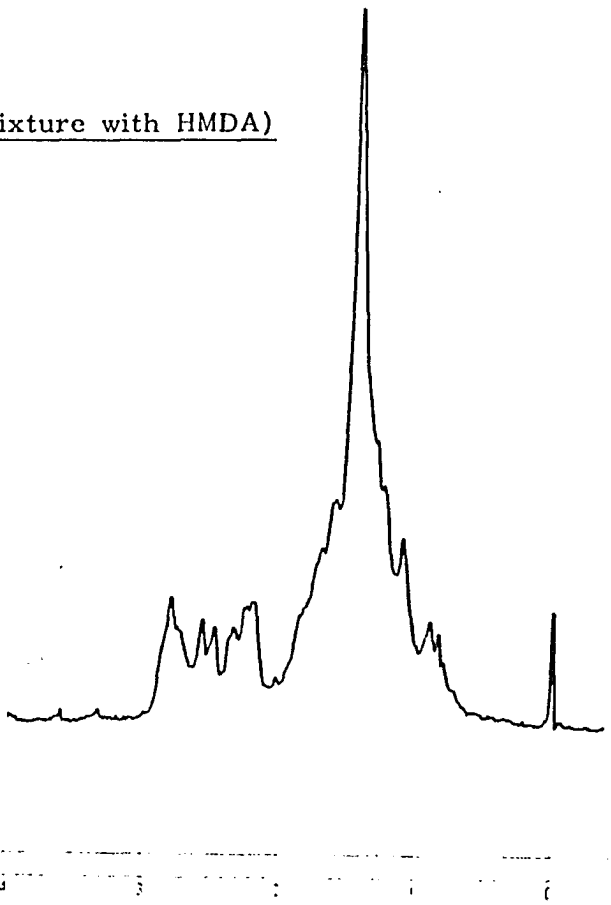


Figure 26

Technical Grade DACH (cis-trans Mixture with HMDA)



shift of the methine protons of trans-DACH is dependent on the degree of protonation. It was also shown that the signal for the methine protons of the dihydrochloride salt of trans-DACH (in $D_2O$) does not overlap with methylene signals. At low pH (about 5), the signal appears at $\delta$3.5 ppm but at high pH (above 11.5), the same signal appears at $\delta$2.35ppm. The methylene signals moved about 0.3 ppm for the same pH range.

The influence of the degree of protonation of the amino group on the chemical shift of the adjacent protons may be general to all amines. The C-1 and C-6 protons of HMDA (in $D_2O$) appear at $\delta$2.60, but the same protons appear at $\delta$3.05 for the dihydrochloride salt.

In some cases, it may be possible to carry out a quantitative

analysis of DACH mixtures by proton NMR in acidic media, making sure that appropriate signals are not overlapping by adjusting the pH. However, such a procedure may result in other difficulties.

The solubilities of the salts of DACH isomers are quite different; (see pp 7-9) and it is possible to separate DACH isomers, as well as other amine components present in the sample, during the salt preparation. If separation does occur, then the quantitative data obtained from proton NMR spectra will not reflect the composition of the original mixture. Since the pH-dependent chemical shift changes are substantial, it may be necessary to prepare a calibration chart for each proton in each possible component so that every signal can be correctly assigned. These difficulties indicate that proton NMR analysis is not suitable as a quick, direct analytical method for the determination of the composition of DACH samples.

## $^{13}C$ NMR Analysis

Since direct analysis of DACH samples by GC and proton NMR did not give satisfactory results, the possibility of using $^{13}C$ NMR spectra to carry out the quantitative analysis was explored. Unlike proton NMR spectra, routine Fourier Transform (FT) $^{13}C$ NMR spectra show signal sizes (integrated areas) that do not necessarily correspond to the number of carbon nuclei present. This is caused by the difference in the relaxation time of various carbon nuclei (resulting in partial saturation of some nuclei) and by the differential nuclear Overhauser effect (NOE) which enhances the carbon signals in the proton-decoupled spectra.[94,95] However, these differences are expected to be small when similar carbon atoms of closely related stereoisomers are compared with each other. Thus it should be possible to obtain the

DACH cis/trans isomer ratio by comparing the peak size for signals due to carbon atoms bearing amine groups ($\alpha$-carbon) of cis-DACH with that of the corresponding signals for trans-DACH. Peaks for $\beta$-carbons and $\gamma$-carbons should be equally useful in determining the isomer ratio.

An alternate approach would be to minimize the effects of differential relaxation time and NOE in proton-decoupled $^{13}C$ NMR spectra by the appropriate choice of experimental conditions. With sufficiently long pulse delays between scans, the saturation effects of carbon nuclei with long relaxation times can be obviated. NOE can be effectively suppressed by using a gated decoupling mode along with moderate pulse delays. It might also be possible to use chemical relaxation reagents to achieve these results without long pulse delays.[94]

The use of $^{13}C$ NMR spectra for quantitative analysis is particularly attractive because of the wide carbon chemical shift range (about 200 ppm) compared with the proton chemical shift range (about 10 ppm). A wider range allows better separation of individual signals.[94] Dihydrochloride salts of DACH isomers give three distinct pairs of $^{13}C$ signals. NMR analysis using these signals has been suggested.[96]

The chemical shifts of DACH and TMDACH are given in Table 6.

Table 6

$^{13}C$ Chemical Shifts ($\delta$ $CDCl_3$ in ppm)

| | | C-1,2 | C-3,6 | C-4,5 | N-Me |
|---|---|---|---|---|---|
| DACH | cis | 52.4 | 31.4 | 22.4 | |
| | trans | 58.2 | 36.0 | 26.0 | |
| TMDACH | cis | 65.5 | 26.9 | 23.3 | 44.3 |
| | trans | 64.0 | 25.7 | 23.1 | 40.1 |

The peaks for cis-DACH appear upfield of the corresponding trans-DACH peaks. This is typical of 1,2-disubstituted cyclohexanes and similar relationships are found, for example, in dimethylcyclohexane, cyclohexanediol, and dichlorocyclohexanes.[94] In the case of dimethylcyclohexane, the enhanced shielding (upfield shift) is attributed to steric compression associated with $\gamma$-gauche interactions of the methyl groups. In the trans-1,2-isomer, there is only one such interaction. However, there are three gauche interactions in the cis-1,2-isomer and the chemical shifts of carbon nuclei in the cis isomer experience larger upfield shifts compared to those of the trans isomer (Fig. 27).

Figure 27

Gauche Interactions in Dimethylcyclohexane Isomers

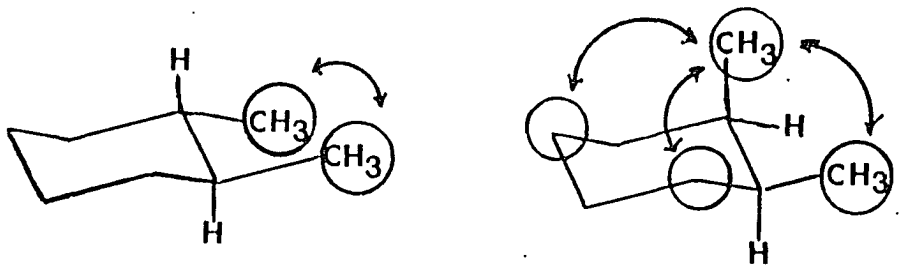
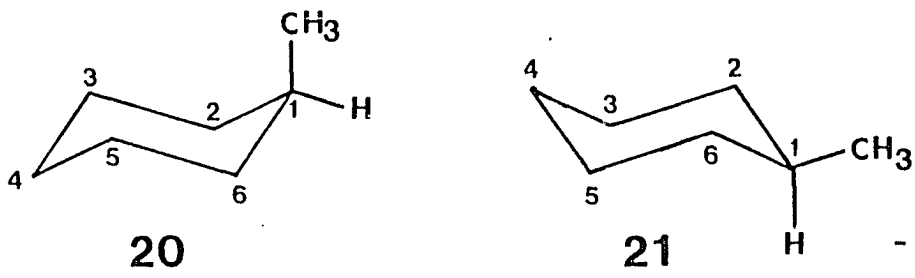



Figure 28

Methylcyclohexane Conformers




20 21

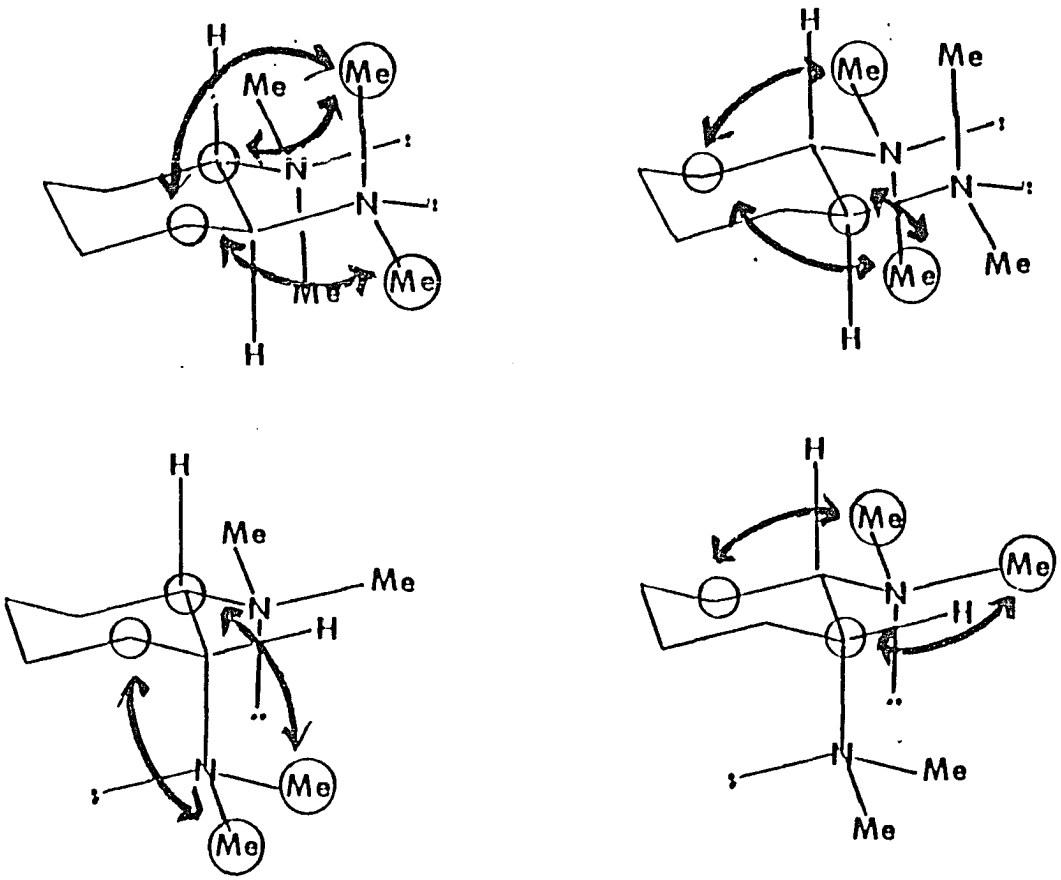
In methylcyclohexane, all peaks for the axially substituted isomer, 20 , appear upfield of the corresponding peaks for the equatorially substituted isomer, 21 (Fig. 28). The upfield shift of the C-3 and C-5 peak of 1-axial methylcyclohexane is especially notable; it is more than 5 ppm upfield of the parent cyclohexane peak. This effect is known as the $\gamma$ shift or "steric shift". The origin of this large upfield shift is not clear. The effect is observed even when steric interaction is absent indicating that other factors are also involved.[97,98]

It is interesting that the relative peak positions of cis and trans-DACH isomers become reversed in the tetramethyl derivatives. Upon N-tetramethylation, the peaks of the trans isomer appear upfield of the corresponding peaks of the cis isomer. The introduction of N-methyl groups adds new $\gamma$-gauche interactions at the C-1,2 and C-3,6 positions in both the cis and trans isomers. These new interactions are reflected in the significant upfield shifts of the C-3,6 peaks in TMDACH (Table 6). In the ground-state conformations of cis and trans-TMDACH from the MM2 calculation[99], there are two new $\gamma$-gauche interactions for each of the C-3 and C-6 positions in trans-TMDACH, but only one each in cis-TMDACH (Fig. 29). The N-methyl peak of trans-TMDACH appears upfield of cis-TMDACH for this reason.

In tertiary amines, carbon atoms that are anti-periplanar to the lone pairs of electrons on nitrogen atoms experience significant upfield shifts, as is also the case with proton shifts.[98] In the conformations shown in Figure 29, the C-3 and C-6 carbon atoms are anti-periplanar to nitrogen lone pairs in trans-TMDACH but not in cis-TMDACH. It is not surprising then that the C-3,6 nuclei show much larger upfield shift in the trans isomer than in cis isomer upon N-tetramethylation of

Figure 29

Ground-State Conformations of TMDACH Isomers




DACH. The upfield shift of the trans isomer is large enough to reverse the relative peak positions in TMDACH.

The introduction of N-methyl groups also affects the chemical shifts of the C-1,2 and C-4,5 nuclei by the $\beta$ and $\delta$ effects in TMDACH. N-Methyl substituents cause large downfield shifts of the

carbon bearing the amino group ( $\beta$ effect). The C-1 chemical shift is 50.94 ppm in aminocyclohexane, but it is downfield at 64.28 ppm in dimethylaminocyclohexane.[100] In the cis-4-methylcyclohexylamines, the C-1 atom gives a larger downfield shift for the axial amino-conformer than for the equatorial amino-conformer when nitrogen is dimethylated.[101] The observed downfield shift for the C-1,2 peak is larger in the cis-TMDACH than in the trans-TMDACH, and the relative positions of the C-1,2 peaks in the TMDACH isomers are the reverse of those in the DACH isomers.

N-Methyl substituents affect the chemical shift of the C-3 and C-5 nuclei only slightly in aminocyclohexanes as can be seen in the following chemical shifts: 26.34 ppm for $-NH_2$, 25.68 for -NHMe, and 26.45 for $-NMe_2$.[100] The $\delta$ effect causes small upfield or downfield shift and is dependent on the stereochemistry in a manner which is not well understood.[94] The chemical shift difference between the two TMDACH stereoisomers is very small for the C-4,5 nuclei and it may be just a coincidence that the C-4,5 peak of the trans-TMDACH happens to appear upfield of that of the cis-TMDACH.

Quantitative $^{13}C$ NMR analysis was carried out directly on a solution of commercial DACH rather than on a solution of dihydrochloride salts in order to avoid any complication from fractionation during salt preparation. Table 7 summarizes the results obtained by $^{13}C$ NMR analysis and by GC analysis via tetramethyl derivatives. The results are in good agreement within the limit of experimental accuracy.

In addition to the wide chemical shift range, $^{13}C$ NMR analysis offers another advantage. From the chemical shift data, structural information on the other components present in crude DACH samples can

Table 7

Comparison of DACH Analysis by GC and $^{13}C$ NMR

| | cis | trans |
|---|---|---|
| GC (TMDACH) | 57% | 43% |
| $^{13}C$ (DACH) | 55% | 45% |
| $^{13}C$ (TMDACH) | 55% | 45% |

be obtained directly. The use of a gated decoupling mode provides quantitative data on the impurities present as well.

The time required to accumulate sufficient scans for obtaining a spectrum with a good signal-to-noise ratio (S/N) can be shortened significantly by using highly concentrated solutions of DACH samples (50% solution) in a wide-bore (10 mm OD) sample tube. DACH is sufficiently basic to undergo exchange with the weakly acidic proton in chloroform. Upon standing, a concentrated DACH solution in deuterochloroform may lose its internal lock signal. It is more advantageous to run $^{13}C$ NMR spectra in deuterobenzene. In this solvent deuterium exchange does not occur and a much stronger lock signal is obtained even for very concentrated DACH solutions.

The $^{13}C$ NMR analysis is a rapid and direct way to obtain the isomer ratio for a DACH sample without prior chemical transformation. The spectrum also yields structural and quantitative information on other material present in the DACH mixture. The advantages of this method for the determination of diamine diastereomer ratios have also been noted by others.[96]

## III: DACH N-METHYLATION REACTION

In order to facilitate the GC analysis of DACH, N-methylation by the Eschweiler-Clarke procedure was carried out using the literature method.[91] Integration of the chromatogram of the resulting product mixture gave an isomer ratio that was inconsistent with that obtained from $^{13}C$ NMR spectra. Since the $^{13}C$ NMR data were consistent with other information already available, the faulty GC results were attributed to some difficulty associated with the N-methylation reaction. In order to ascertain the source of this difficulty, the Eschweiler-Clarke N-methylation of DACH mixtures was studied in depth.

### Eschweiler-Clarke N-Methylation Procedure

The reductive alkylation of amines by aldehydes and ketones using formic acid or its derivatives is known as the Leuckart reaction. In particular, a variant of the Leuckart reaction employed to N-methylate primary and secondary amines uses formaldehyde and formic acid in large excess and is known as the Eschweiler-Clarke procedure.[102] The literature procedure for the dimethylation of benzylamine with formic acid and formaldehyde calls for refluxing the mixture for 8-12 hours or two to four hours after gas evolution ceases.[92] In some cases the mixture is refluxed for 24 hours since it is difficult to detect the slow gas evolution from a reaction mixture at reflux.[103]

In this study, initial attempts to N-tetramethylate DACH samples by the Eschweiler-Clarke procedure involved reflux times of 18-24 hours. However, $^{13}C$ NMR spectra of the resulting materials showed that a complex mixture of products and not a simple mixture of the

expected tetramethyl derivatives was produced. A gas chromatogram of this mixture showed the presence of an unexpected product which earlier had been assigned to one of the TMDACH isomers, thus giving rise to a faulty isomer ratio. From $^{13}C$ NMR spectra, it was found that a 24-hour reflux gave complete N-tetramethylation of trans-DACH and all the other amines present. However, the N-tetramethylation of cis-DACH was incomplete and a mixture of tetramethyl and trimethyl derivatives (TMDACH and TriMDACH) was produced. Because of this unexpectedly slow conversion of cis-DACH, the following study of the Eschweiler-Clarke reaction was undertaken.

Study of Timed DACH Methylation

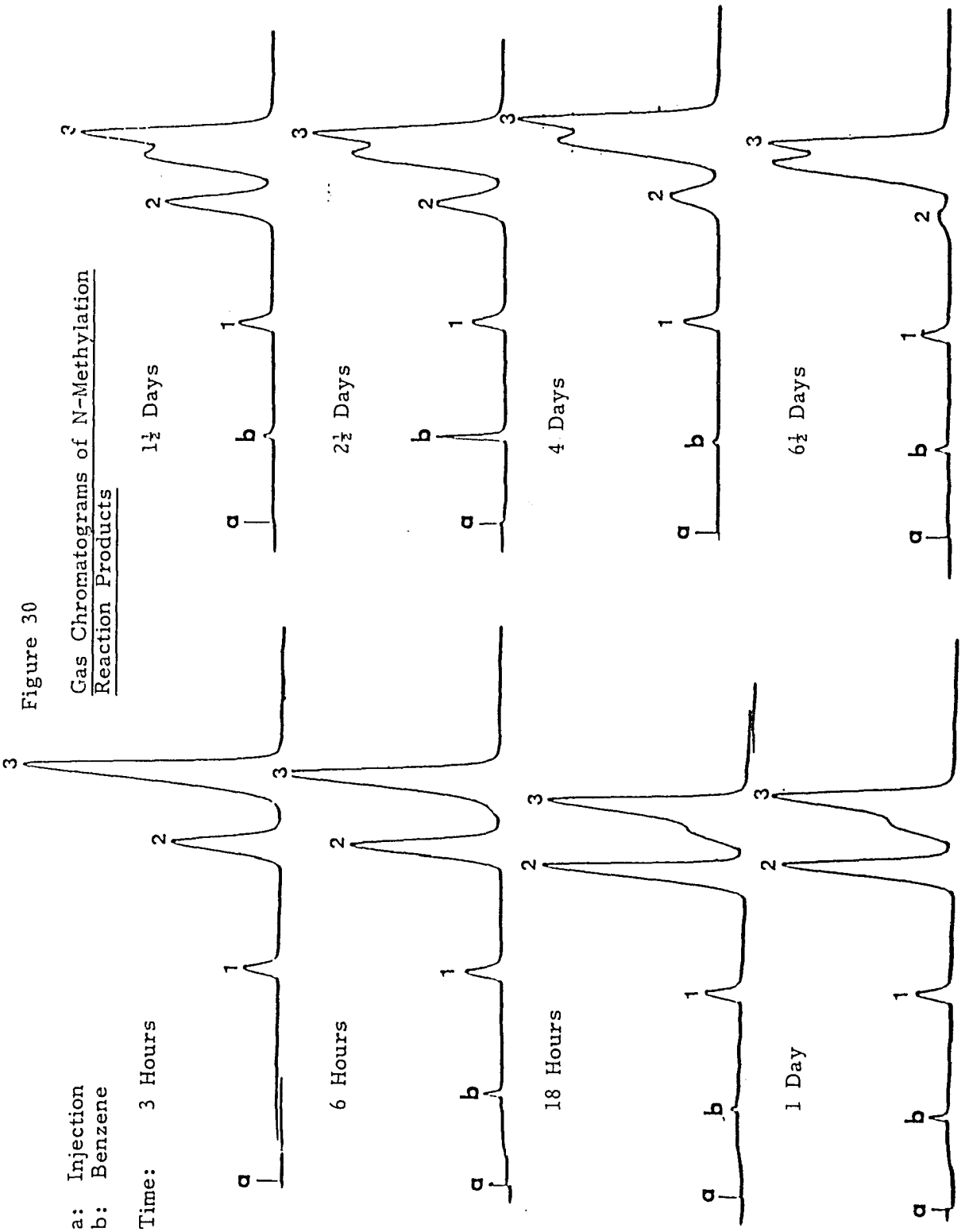
In order to study an unusually slow N-tetramethylation of cis-DACH by the Eschweiler-Clarke procedure, a large scale reaction was carried out; and the progress of the reaction was monitored by working up aliquots from time to time and analyzing the products by GC and $^{13}C$ NMR. The changes in the chromatograms as the reaction progressed are shown in Fig. 30.

At a reaction time of three hours, the chromatogram shows three components. As the reaction time is increased, very little change is observed for peaks 1 and 3, but a striking change takes place for peak 2. The area under peak 2 increases up to a reaction time of 18 hours and then gradually decreases until it is almost negligible at 6½ days. Concurrent with the change in peak 2 area, a leading shoulder appears on peak 3. This shoulder is barely discernable at 6 hours but becomes more prominent as the area of peak 2 decreases, finally becoming the largest peak at 6½ days. The following assignments were made based on $^{13}C$ NMR spectra of samples obtained by preparatory scale GC:

Figure 30

Gas Chromatograms of N-Methylation Reaction Products

a: Injection
b: Benzene



peak 1 - N,N,N',N'-tetramethyl-2-methyl-1,5-diaminopentane (from an impurity in the DACH sample used); peak 2 - cis-TriMDACH; peak 3 - trans-TMDACH. The leading shoulder of peak 3 was found to be cis-TMDACH.

Although baseline separation of peaks was not accomplished, a sufficient resolution of cis and trans-TMDACH was obtained at greatly reduced column temperature and carrier gas flow rate to make a calculation of the cis/trans isomer ratio possible. Although the separation of TMDACH isomers is difficult on a basic Carbowax column, there is a clean separation of cis-TriMDACH from TMDACH isomers. It is possible that other workers may have made an incorrect peak assignment for similar chromatograms; indeed an incorrect assignment was made initially in this study. Making the erroneous assumption that the cis-TriMDACH peak represents quantitatively the amount of cis-TMDACH present leads to a cis/trans-DACH ratio heavily biased toward trans isomer for methylations by the Eschweiler-Clarke procedure with a refluxing period under 24 hours. In fact, the supplier of this particular DACH sample (97% pure, isomer ratio found to be 55 cis - 45 trans) reported the ratio as 30 cis - 70 trans.

From this study, it is clear that the Eschweiler-Clarke N-methylation of cis and trans-DACH proceeds at quite different rates for the two diastereomers. Unless one takes care to ensure that the reactions for both isomers are complete (at least 7 days refluxing under a normal Eschweiler-Clarke procedure or 3-4 days under forcing conditions[22]), the resulting GC data can be exceedingly misleading. It may be surmised that much of the erroneous analytical data provided by suppliers has resulted from a misinterpretation of the chromatograms for

N-methylation mixtures.

Axial Effect

From changes in cis/trans ratios of TMDACH, determined from $^{13}C$ spectra, the half-time of the cis-DACH tetramethylation is estimated to be about 35 hours (Fig. 31). After three hours of refluxing trans-DACH under Eschweiler-Clarke conditions, only TMDACH is observed. From this evidence, the half-time for trans-DACH tetramethylation is estimated to be less than one hour. Thus the rate of formation of the tetramethyl derivative of cis-DACH is probably at least one-fiftieth (1/50) that of trans-DACH.

The observed difference in the N-tetramethylation rates for the DACH diastereomers is an example of an "axial effect". It is well known that in transformations which increase steric congestion in the products compared to the starting materials, axial groups undergo reactions more slowly than equatorial groups. In such reactions, transition state energies for conversion of axial groups are greater than those for conversion of equatorial groups. The methylation of 22 takes place about 50 times faster than that of 23 [104] (Fig. 32). The reduced reaction rate of axial amino compounds is a reflection of the increased steric hindrance caused by two 1,3-diaxial hydrogens which impede the approach of the methylating agent (Fig. 33).

In cis-DACH, one of the amino groups is always axial and thus the cis isomer is expected to show some decrease in the tetramethylation rate compared to trans-DACH in which both amino groups are equatorial[93] (Fig. 34).

Figure 31

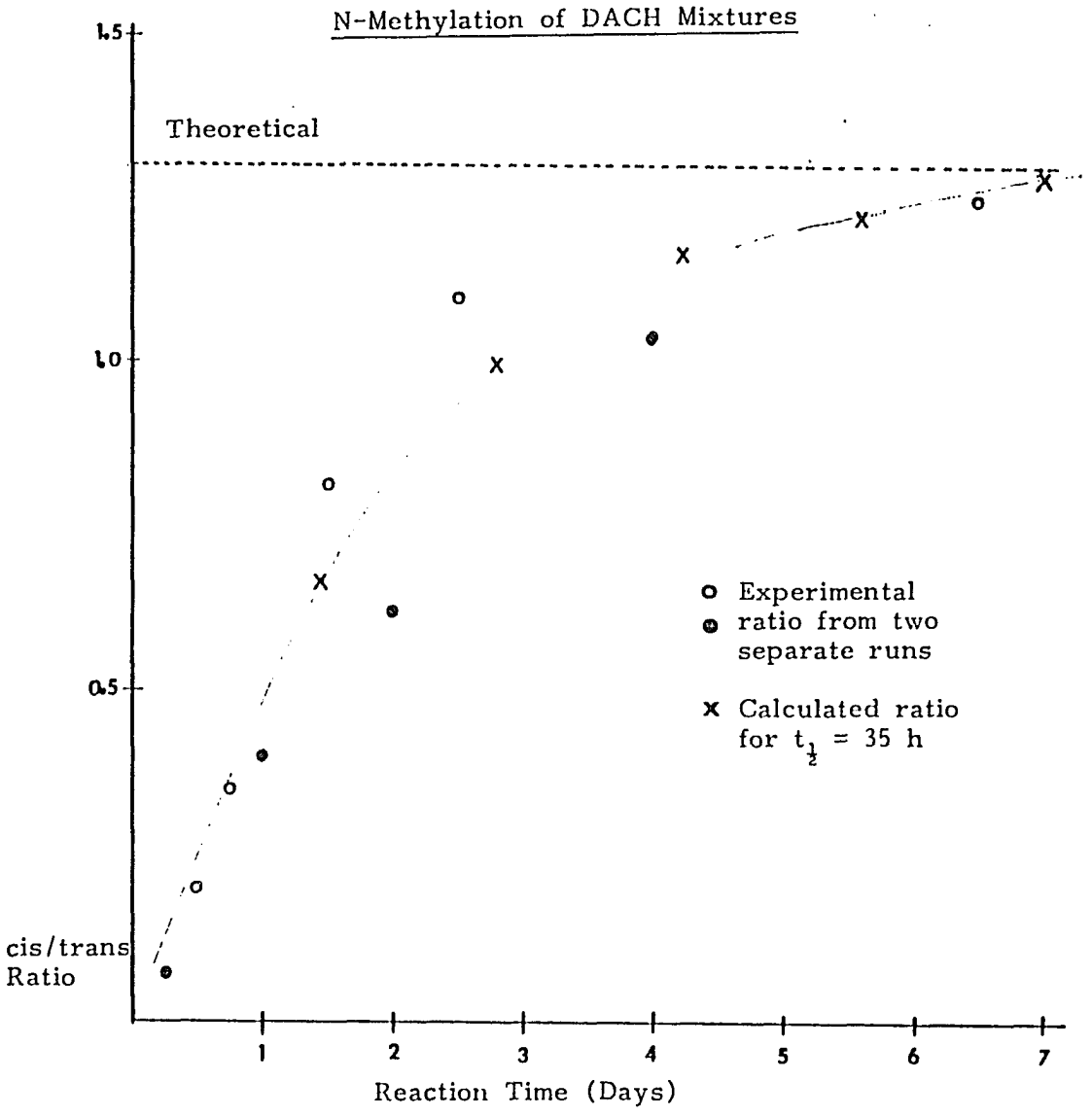
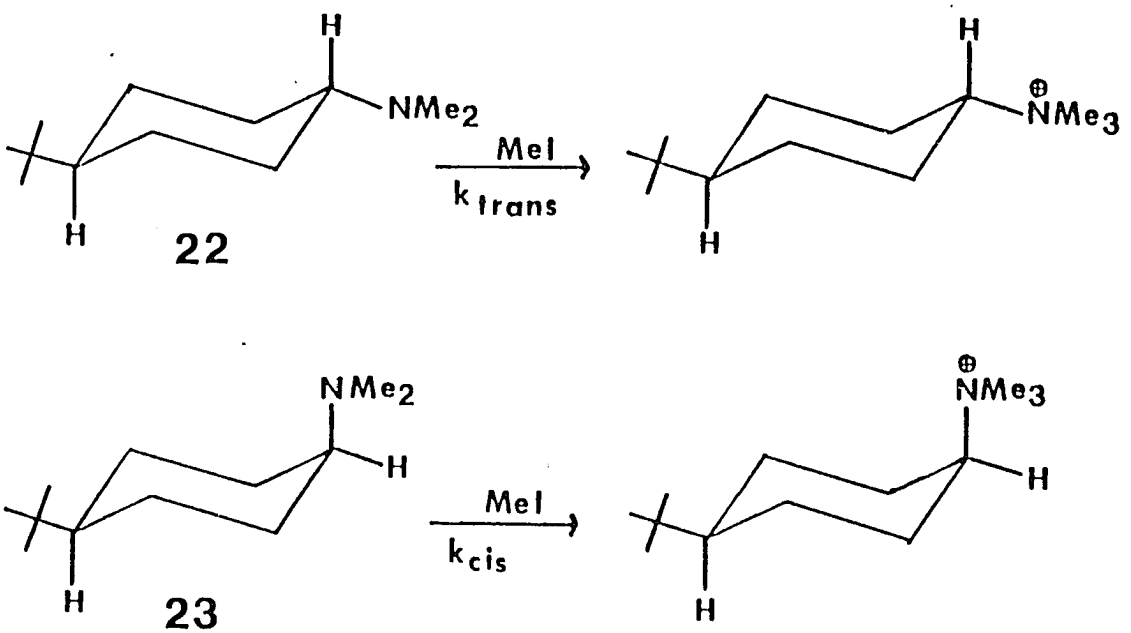


Figure 32

Axial Effect




$$k_{rel} = \frac{k_{trans}}{k_{cis}} \approx 50$$

Figure 33

1,3-Diaxial Interaction

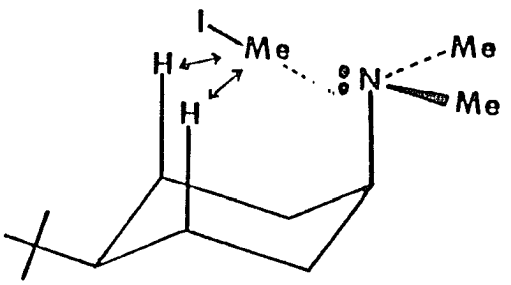
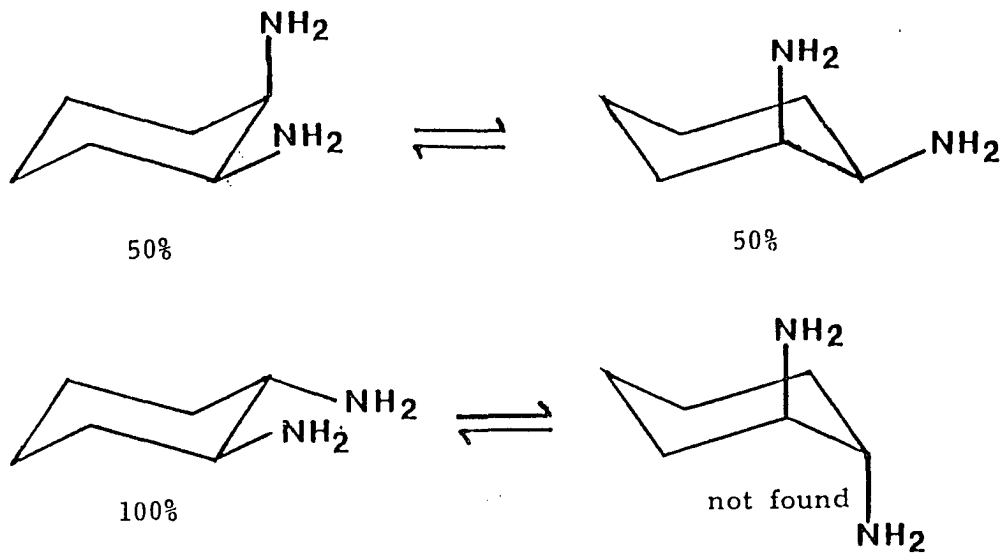


Figure 34

Conformational Equilibria of DACH Isomers



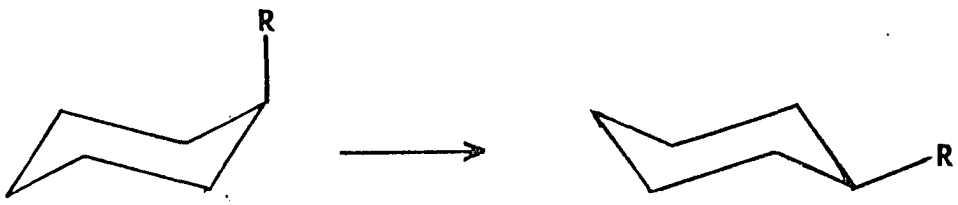

Methylation of TriMDACH

GC and $^{13}C$ NMR data show that the slowest step of the N-tetramethylation of cis-DACH by the Eschweiler-Clarke procedure is the conversion of TriMDACH to TMDACH. The slowness of this step is attributed to two factors: an unfavorable equilibrium distribution of the more reactive conformer and the axial effect, which impedes the reaction of the more abundant conformer.

The preference of a cyclohexane substituent to occupy an equatorial position over an axial position is expressed as the A-value, which is $-\Delta G^{\circ}$ for the transformation shown in Fig. 35. The smaller A-value of the methylamino group compared with the dimethylamino group indicates that the former has less preference for the equatorial position than the latter.[101] Thus in the equilibrium shown in Fig. 36, the conformation with an axial methylamino group ( 24 ), is favored over the conformation with an axial dimethylamino group ( 25 ).

Figure 35

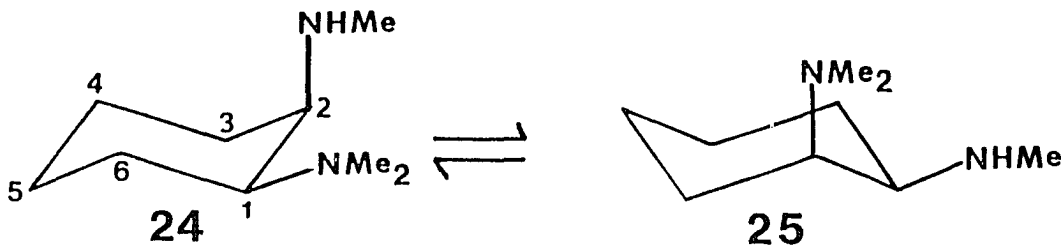
A-Values of Cyclohexylamines




| R | A-Values |
|---|---|
| NHMe | 1.29 (195°K) |
| $NMe_2$ | 1.53 (183°K) |

Figure 36

cis-TriMDACH Conformational Equilibrium




24 is expected to show decreased reactivity since the reactive group is axial. Therefore the rate of conversion of 24 to TMDACH is expected to be considerably slower than the similar conversion of the corresponding trans-DACH derivative.

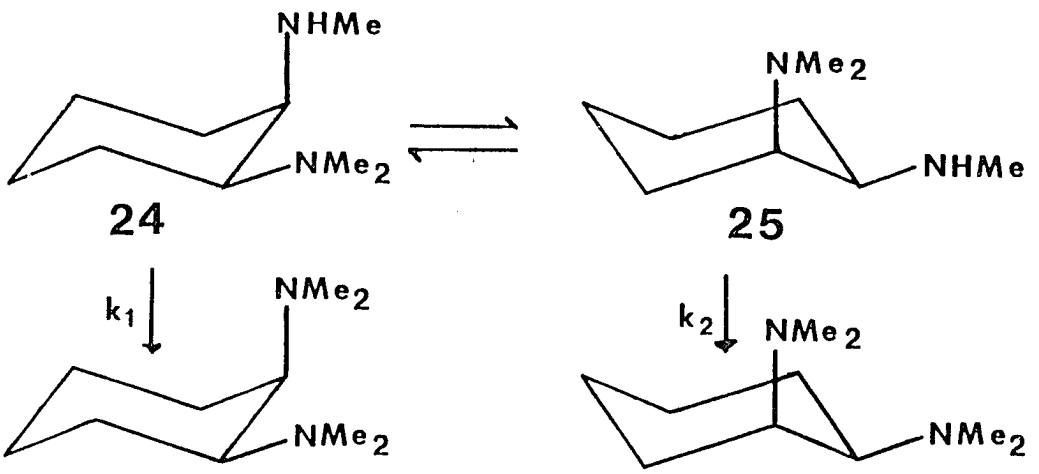
The reactivity of 25, with the reactive group in an equatorial position, is expected to be comparable to that of the corresponding trans-DACH derivative. However, since 25 is a minor conformer, the formation of TMDACH from 25 is expected to be slow under the pseudo-first order kinetics assumed for the Eschweiler-Clarke procedure with a large excess of reagents.

These two factors then make the over-all rate of cis-TMDACH

formation significantly slower than the formation of trans-TMDACH. This is not intended to be a rigorous argument, but merely a rationale for the observed slow N-tetramethylation of cis-DACH compared with that of trans-DACH based on a simplified reaction scheme shown in Fig. 37.

Figure 37

Formation of cis-TMDACH




$$\text{Rate} = k_1[\underset{\sim}{24}] + k_2[\underset{\sim}{25}] = k_1[\underset{\sim}{24}] + k_2 K_{eq}[\underset{\sim}{24}] \qquad K_{eq} = [\underset{\sim}{25}] / [\underset{\sim}{24}]$$

$K_{eq}$ and $k_1$ are relatively small. $\Longrightarrow$ Rate is relatively small.

A-values given for methylamino and dimethylamino groups cannot be used to calculate the relative population of the two conformers of cis-TriMDACH under the Eschweiler-Clarke conditions. A-values are temperature-dependent and are expected to be larger at the relatively high temperatures of the Eschweiler-Clarke procedure than at lower temperatures (below 200°K).[101,105] However, how the temperature affects each A-value is not known and the equilibirium constant and the

conformer distribution at the reaction temperature cannot be calculated from the available data.

It should also be noted that the A-values given are calculated from equilibrium constants for the conformational equilibria of 4-alkylcyclohexylamines. These values are not strictly applicable to vicinal diaminocyclohexanes since the experimental values do not take into account any 1,2-diamine interactions.

Using empirical shift parameters, $^{13}C$ chemical shifts can be calculated to assist in the structural identification of organic compounds. Table 8 gives the calculated chemical shifts of ring carbons in the two conformers of cis-TriMDACH (based on the parameters for cyclohexylamines reported by Booth et al.[101]) along with the chemical shifts observed at ambient temperature. The observed chemical shifts fit better for 24, but the chemical shift differences for the two confomers are too small for such a conclusion and it is meaningless to estimate the equilibrium distribution of two conformers. The small differences in the chemical shifts of the two conformers arise from opposing effects of similar magnitude. For example, a C-1 atom experiences an upfield shift of 3.4 ppm due to the axial $\alpha$-dimethylamino group in 25, but in 24 the same carbon experiences an upfield shift of 3.7 ppm due to the $\beta$-methylamino group at the axial position. These two opposing effects result in very small chemical shift differences (67.0 ppm for 24; 67.3 ppm for 25). It is interesting to note that the magnitudes of the two steric shifts are not the same for a C-2 atom. In 24, the axial $\alpha$- methylamino group produces an upfield shift of 5.1 ppm but that due to the axial $\beta$-dimethylamino group is only 0.5 ppm, giving calculated shifts of 55.9 ppm for 24 and 60.5 for 25. The C-2

carbon is the only one that shows significant chemical shift differences and the agreement of the observed chemical shift of this carbon compared to that calculated for 24 is remarkable (Table 8).

Table 8

| Calculated Chemical Shifts | | Observed Chemical Shifts |
|---|---|---|
| **24** | **25** | |
| 67.0 | 67.3 | 67.5 |
| 55.9 | 60.5 | 55.8 |
| 28.2 | 26.3 | 27.5 |
| 25.5 | 26.2 | 25.5 |
| 23.0 | 24.8 | 25.2 |
| 18.9 | 18.5 | 19.0 |

In order to carry out a rigorous analysis of the kinetics of these methylation reactions, more information on the reaction rates of various steps in the process are needed. With the limited data available at this time, such a discussion is not possible and the simplified view presented must suffice.

Reactivity of cis-DACH

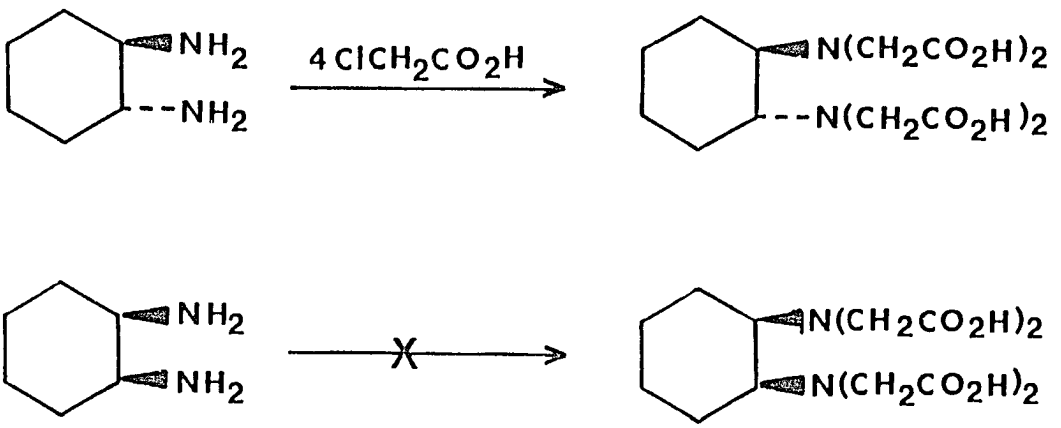
The possible grounds for the slow N-tetramethylation of cis-DACH are discussed in the previous section. In light of these findings the reported failure to obtain the tetraacetic acid derivative of cis-DACH, using a method which was used successfully to prepare that of trans-DACH[66] is understandable (Fig. 38).

It is important to verify the completeness of the chemical conversion of each isomer in the GC analysis of DACH derivatives.

There are a number of ways of preparing N-methylated amines for GC analysis which are reported to be simpler and more rapid than the Eschweiler-Clarke procedure,[106-109] but it is necessary to test these methods for the quantitative conversion of each isomer before applying them to the analysis of DACH. Such a verification has not been reported for the GC analysis of DACH after trifluoroacetylation and therefore, this reported analytical method[110] may not be accurate.

Figure 38

Formation of DACHTA



## IV: ASYMMETRIC SYNTHESIS WITH CHIRAL DACH DERIVATIVES

In the past decade, asymmetric synthesis has become one of the most intensely studied synthetic methodologies.[111-115] It is especially relevant to the total synthesis of complex natural products in which synthetic strategy needs to take into account control of the absolute stereochemistry.[116] Asymmetric synthesis is formally defined as "a reaction in which an achiral unit in an ensemble of substrate molecules is converted by a reactant into a chiral unit in such a manner that the stereoisomeric products are produced in unequal amounts."[111] Earlier, in Section I, examples of asymmetric syntheses using chiral DACH and its derivatives have been cited. These examples included asymmetric hydrogenation with a soluble rhodium complex of chiral aminophosphines and alkyllithium addition to aldehydes and ketones in the presence of TMDACH. (See pp 36-38.)

One area of asymmetric synthesis of special interest to this author is asymmetric reduction with chiral metal hydride reagents.[117] Previous studies of modified borohydride reagents and lithium aluminum hydride reagents modified with aminodiols have been reported elsewhere.[118-119] In this study, three derivatives of chiral DACH were prepared and asymmetric ketone reduction using lithium aluminum hydride reagents modified with these new chiral ligands were investigated.

### Asymmetric Reduction

Lithium tetrahydridoaluminate (more commonly called lithium aluminum hydride and symbolized as $LiAlH_4$ or LAH) is a useful reagent for the reduction of ketones to secondary alcohols.[120] By replacing

one or more of the hydrogens in LAH with chiral ligands, chiral reagents of the type $LiAlH_{4-n}L^*_n$ (n = 1, 2, or 3; $L^*$ = chiral ligand) are obtained. When these chirally modified reagents are allowed to react with unsymmetrical ketones, enantiomeric alcohols may be formed in unequal amounts. These reagents can also be used to obtain isotopically labeled chiral primary alcohols by the asymmetric reduction of deuterium (or tritium)-labeled aldehydes. Alternatively, chiral primary labeled alcohols can be obtained by the asymmetric reduction of unlabeled aldehydes by chirally modified LAD (or LAT) reagents.

In the earliest reports of asymmetric reductions by chirally modified LAH reagents, alcohols such as (-)-menthol, (-)-borneol and (-)-isoborneol were used as chiral modifying ligands. These reagents gave only a small amount of asymmetric induction (less than 5% e.e.).[121] However, in the reduction of aminoketones, an exceptionally high degree of asymmetric induction by these reagents was noted. It is known that the reduction of ketones by LAH is assisted by the electrophilic coordination of the carbonyl oxygen by the lithium cation. It is thought that in the reduction of $\alpha$- and $\beta$-aminoketones, the lithium cation is also coordinated to a nitrogen atom to form a five- or six-membered chelate ring. A reduction proceeding via such cyclic intermediates is thought to be capable of enhanced stereoselectivity.[117]

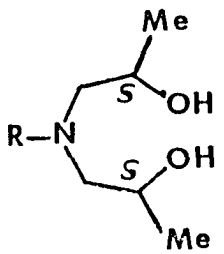
The coordinating heteroatom (which can be oxygen or nitrogen, but not sulfur[117]) can be a part of the ketone substrate, as in the cases cited above, or it can be part of the chiral ligand.

With aminodiols 26 and 27 intermediate complexes such as 28, formed by the coordination of a lithium ion to the ligand and to the substrate, have been proposed (Fig. 39). Examination of space-

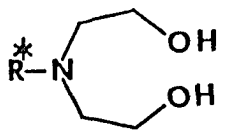
filling models showed that nitrogen and two oxygens of the dihydroaluminate intermediate form a pocket into which a lithium ion can fit perfectly. The lithium ion can further coordinate with the carbonyl oxygen of substrate ketones to form a tight complex between reducing agent and substrate.

Figure 39

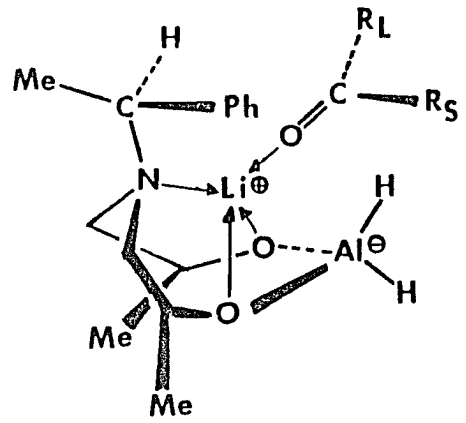
Aminodiols and Intermediate Complex




26




27




28

R = nBu, tBu

R* = (R)- *CH(CH$_3$)Ph

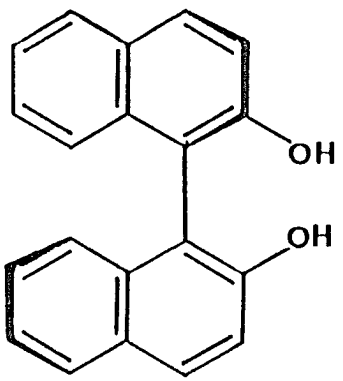
(R)- or (S)- *CH(CH$_3$)Ph

LAH modified with 29 and 30 (Fig. 40) gives reagents that are highly effective and are reported to give secondary alcohols with better than 95% e.e.[122-127] With such a success, one would expect a wide application of asymmetric reduction with modified LAH reagents in organic synthesis. A number of synthetic applications of these reagents in the small scale preparation of natural products has been reported.[120] However, no large scale application of modified LAH asymmetric reduction has been reported.[128]

The factors limiting the wide application of this method have been discussed elsewhere.[117] One difficulty with Mukaiyama's modifiers ( 30 ), in synthetic applications is that these ligands are prepared from naturally occuring (S)-proline and thus only one enantiomer of each ligand is readily available. Therefore the chiral sense of the hydride transfer is limited to the production of only one absolute configuration, even if it is not the desired configuration. This is also true of many other LAH modifiers such as Darvon alcohol, N-methylephedrine, quinine and other alkaloids. DACH, on the other hand, is a convenient and versatile starting material for the preparation of chiral diamine modifiers since both enantiomers of DACH are readily available.

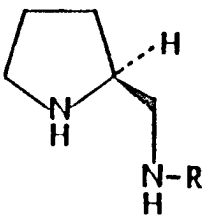
Figure 40

Chiral LAH Modifiers




29

R = Ph
R = isopropyl
R = hexyl
R = cyclohexyl
R = (R)-1-phenylethyl
R = (S)-1-phenylethyl
R = 1-naphthyl




30

R = 2-methoxyphenyl
R = 4-methoxyphenyl
R = 2-pyridyl
R = 4-pyridyl
R = 3,4-dichlorophenyl
R = 2,6-dimethylphenyl

Preparation of Chiral Derivatives of DACH

N,N'-Dialkyl DACH derivatives have been prepared by a round-about route rather than by a direct alkylation of DACH with alkyl halides, since it is difficult to control the alkylation of diamines to obtain only the N,N'-dialkyl product.[129]

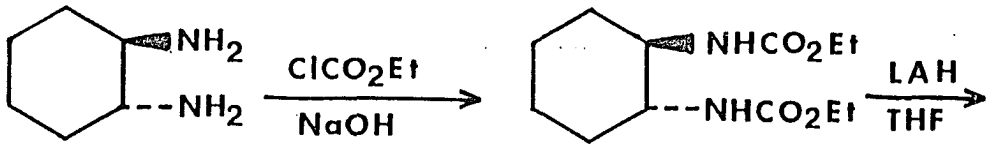
Reactions of (-)-(R,R)-DACH with ethyl chloroformate[82] and acetic anhydride[130] yielded the corresponding biscarbamate and diamide, respectively. LAH reduction of these products leads to the formation of N,N'-dimethyl-DACH (DMDACH) and N,N'-diethyl-DACH (DEDACH) as shown in Fig. 41. Reported yields for the LAH reduction step were only moderate; overall yields were 54% for DMDACH (as the dihydrochloride salt) and 31% for DEDACH. Reduction of the biscarbamate required a large excess of LAH (10g LAH for 9g substrate) and a long refluxing period.[82] The dibenzamide of DACH was also prepared but its LAH reduction to N,N'-dibenzyl-DACH (DBDACH) was unsuccessful because it was highly insoluble in suitable organic solvents.[131]

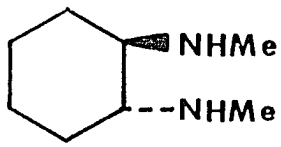
In this study, DBDACH was prepared by $NaBH_4$ reduction of the diimine prepared from DACH and benzaldehyde (Fig. 42). Although the yield of crude DBDACH was 99%, the yield of pure product was only 71% because the high-boiling DBDACH underwent some decomposition during the final distillation step (bp 213-214°C at 0.7 mmHg). In this two step synthesis, the crude diimine was isolated before the reduction step, since the one-pot reductive alkylation of DACH with benzaldehyde might lead to an undesirable mixture of mono-, di-, tri-, and tetra-alkyl products.[132]

Racemic trans-DPHHQ was prepared from a commercial DACH mixture and benzil by a literature method.[21] It was reduced with

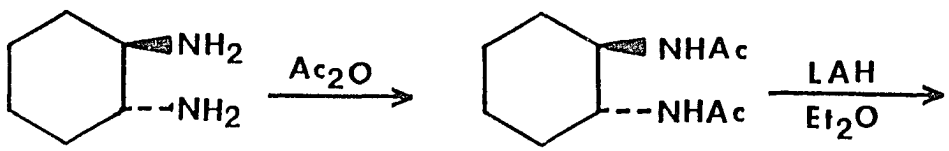
Figure 41

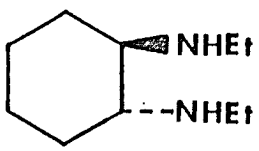
Synthesis of N,N'-Dialkyl DACH




DMDACH

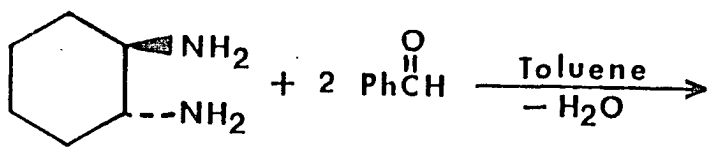


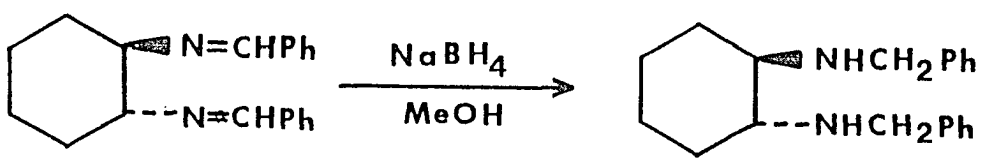




DEDACH

Figure 42

Synthesis of DBDACH



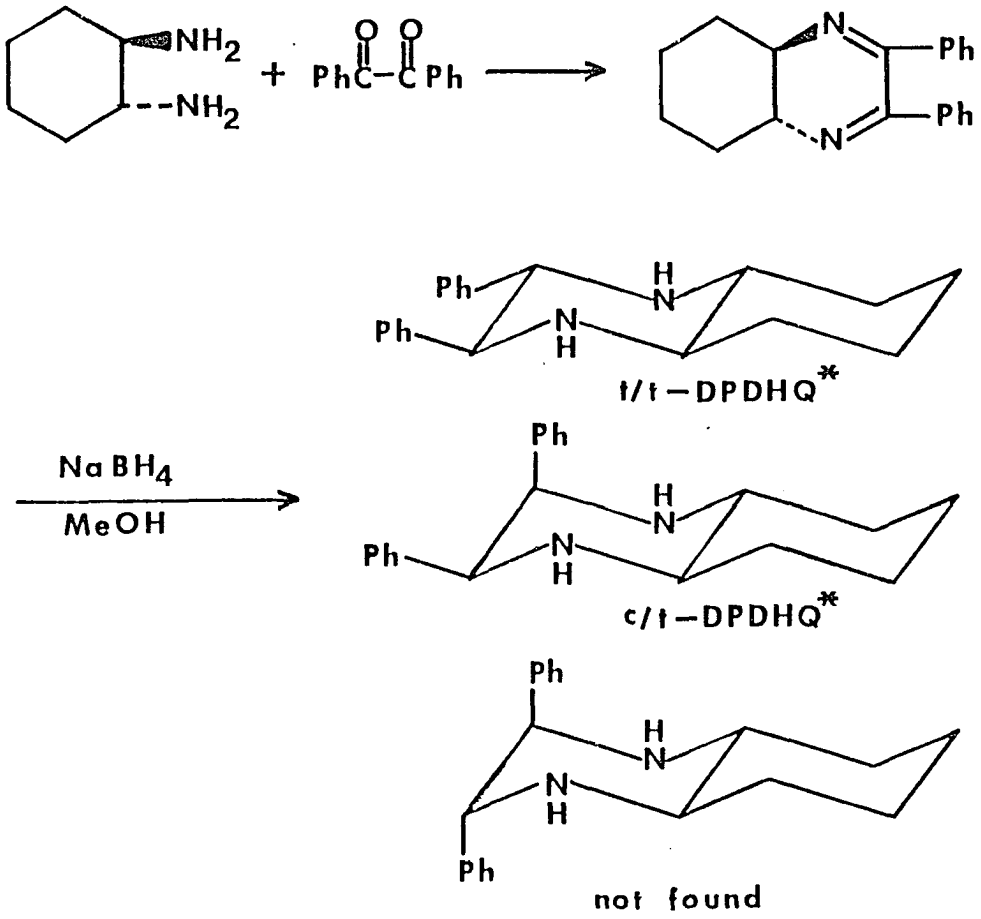

DBDACH

$NaBH_4$ in methanol to a mixture of 2,3-diphenyldecahydroquinoxaline (DPDHQ) diastereomers (designated as t/t and c/t isomers; Fig. 43) in 96% yield. The t/t:c/t isomer ratio was 79:21. A third possible diastereomer was not observed. The two diastereomers present were easily distinguished by proton NMR. The symmetrical t/t isomer showed a singlet for the benzylic protons at $\delta$3.82; the unsymmetrical c/t isomer shows a pair of doublets at $\delta$4.17 and 4.63 (J = 7 Hz). The integration of the peak areas of these signals provided the isomer ratio in the mixture. During the hydrolysis of excess hydrides as part of the reaction workup, the dihydrochloride salt of the t/t isomer selectively precipitated out of the reaction mixture. The workup of this precipitated salt separately from the rest of the reduction product still in solution, gave pure t/t isomer in 70% yield. It was further purified by recrystallization from aqueous ethanol. From the remaining reduction mixture, a product now enriched in c/t isomer was obtained. However, the c/t isomer could not be isolated in pure form by fractional recrystallization or by thin layer chromatography.

An analogous reaction of (-)-(R,R)-DACH with benzil gave optically active trans-DPHHQ (DPHHQ*). The $NaBH_4$ reduction of DPHHQ* in methanol gave a mixture of two optically active diastereomers, t/t-DPDHQ* and c/t-DPDHQ*, in a 78:22 isomer ratio. Again, the dihydrochloride salt of t/t-DPDHQ* selectively precipitated out of the reaction mixture during the workup. t/t-DPDHQ* was purified by slow recrystallization from methanol-water. Since the $NaBH_4$ reduction of DPHHQ was found not to be a suitable method for the preparation of pure c/t-DPDHQ, the reduction of DPHHQ* was attempted with various reagents in the hope that a reduction system that would give a higher

Figure 43

Synthesis of DPDHQ




percentage of the c/t isomer could be found.

Stereoselective Reduction of DPHHQ

Although the stereochemistry of carbon-oxygen double bond reductions has been extensively studied, there have been only a few stereochemical studies of carbon-nitrogen double bond reductions.[133-135] Yet the stereoselective reduction of cyclic imines would provide a convenient entry into various biologically active indolines and

isoquinoline alkaloids.[136-137] Imines are not as stable as ketones and aldehydes and are more susceptible to hydrolysis, polymerization and isomerization to enamines.[138] There is also the added complication of syn-anti isomerization. Perhaps these factors have discouraged systematic investigations. In the reduction of an imine carbon-nitrogen double bond, reagents exhibit different stereoselectivities and these are sometimes quite different from those observed for carbonyl reductions.[135] In a preparation of chiral fluoroalkylated amines, Pirkle et al. studied the stereoselectivity of imine reduction with a number of reducing agents. It was demonstrated that the diastereomer ratio of the product mixture can be varied widely by adjusting the reaction conditions.[139] Similarly, in the present work a series of DPHHQ* reductions was carried out. The results are summarized in Table 9.

For the $NaBH_4$ reduction in methanol, a large volume of solvent was used initially since DPHHQ* is not very soluble in methanol (~1g in 200 mL MeOH). However, the reduction of DPHHQ* suspended in methanol was found to be just as effective as reduction in a homogeneous solution. It is necessary to use a large excess of $NaBH_4$ since the hydride reacts with the solvent, but the reaction can be monitored visually. The substrate DPHHQ* is bright yellow; the t/t- and c/t-DPDHQ* mixture is colorless.

Reductions with dimethylamine borane ($DMA{\cdot}BH_3$) and $NaBH_3CN$ in acetic acid gave similar results. In these cases the product diastereomer ratio was the reverse of that obtained using $NaBH_4$. Undoubtedly reduction is preceded by protonation in an acidic medium and therefore hydrogen transfer is actually to an iminium ion. It is fortunate that the reaction is very rapid (~15 minutes) because the starting material is

Table 9

Stereoselectivity of DPDHQ* Reduction

| Reducing Agent | % yield | % t/t-DPDHQ* | % c/t-DPDHQ* |
|---|---|---|---|
| 1. $NaBH_4$/MeOH | 95 | 78 | 22 |
| 2. DMA•$BH_3$/AcOH | 91 | 20 | 80 |
| 3. DMA•$BH_3$/THF, HCl | 86 | 21 | 79 |
| 4. $NaBH_3CN$/AcOH | 88 | 20 | 80 |
| 5. $BH_3$/THF | 98 | 27 | 73 |
| 6. Na°/EtOH | | no reduction | |
| 7. $NaBH_4$, LiBr/$Et_2O$ | | no reduction | |
| 8. $NaBH_4$, LiBr/THF | 62 | 61 | 39 |
| 9. $LiAlH_4$/$Et_2O$ | 98 | 2 | 98 |

not very stable in acidic media. DMA•$BH_3$ has been reported to reduce imines in THF,[140] but there was no observable reduction of DPHHQ* after 9 days of refluxing. However, rapid reduction took place when an aqueous HCl solution was added to the reaction mixture. DMA•$BH_3$ is an effective reducing agent for aldehydes and ketones, although it is not used as widely as $NaBH_4$ or $LiAlH_4$.[141] Trimethylamine borane (TMA•$BH_3$), in contrast, is much less reactive and reportedly does not reduce cyclohexanone in THF at room temperature. Interestingly, TMA•$BH_3$ rapidly reduces cyclohexanone when aqueous HCl is added.[142]

The stereochemical result of the $BH_3$/THF reduction is similar to that of other borane reagents, but the yield is better, perhaps reflecting the instability of the starting diimine in acetic acid. In this case, $BH_3$ may be acting as a Lewis acid and coordinating with imine nitrogen, since nitrogen is a better donor atom than oxygen.

The $Na^o$/EtOH reduction of an imine is an old procedure,[133] but no reduction of DPHHQ* was observed with this system at room temperature.

A $LiBH_4$ reagent was prepared in situ by stirring solid $NaBH_4$ and anhydrous LiBr in $Et_2O$ and THF. The $LiBH_4/Et_2O$ reagent gave no DPHHQ* reduction and titration of the reagent solution showed that very little hydride was present. It has been reported that reagent formation in $Et_2O$ sometimes does not take place smoothly, but is more facile in THF.[143] The reduction of DPHHQ* with $LiBH_4$ in THF was more successful, but the yield was still low.

Compared with $NaBH_4$ reduction of DPHHQ* in methanol (2 hours), LAH reduction in ether was very slow (over 3 days). Generally LAH is much more reactive than $NaBH_4$. It may be that in hydroxylic solvents, the imine is activated by solvent hydrogen-bonding (similar to activation via proton-transfer to form an iminium ion) and the reduction rate is increased. The LAH reduction gave a nearly pure c/t-DPDHQ* in high yield. Analytically pure c/t-DPDHQ* was obtained by washing its dihydrochloride salt repeatedly with cold methanol-ether.

Modified LAH Reagents from DACH Derivatives

Modified LAH reagents were prepared from the newly prepared chiral diamines (DBDACH, t/t- and c/t-DPDHQ*) by treating a suspension of solid lithium aluminum hydride with an ether solution of diamine (1.1 equivalents) at 0°C. Propiophenone, a common substrate for this type of study, was reduced at -78°C and the degree of asymmetric induction caused by each of these chiral reagents was determined from the optical rotation of the resulting alcohol. The results are summarized in Table 10.

Table 10

Asymmetric Reduction of Propiophenone with LAH Modified with Chrial DACH Derivatives

| Modifier | % Propiophenone Reduction | Product % e.e. | Configuration of Predominant Enantiomer of Product |
|---|---|---|---|
| DBDACH | 97 | 36 | R |
| t/t-DPDHQ* | 100 | 1 | S |
| c/t-DPDHQ* | 100 | 4 | S |

All three chirally modified LAH reagents are effective reducing agents, but only the DBDACH-LAH reagent gave any significant asymmetric induction. The modest degree of asymmetric induction with propiophenone suggests that these three diamines are probably not good candidates for further systematic study. However, it is always possible that some recipe might be found for their incorporation into a useful system. In this connection it is worth noting that in studies by Noyori and co-workers, the exceptionally high asymmetric induction was observed with a binaphthol-LAH reagent (for the reduction of acetophenone) only if an achiral comodifier (ethanol was best) was added. Without the comodifier, acetophenone reduction gave 1-phenylethanol with only 2% e.e. and opposite configuration.[122-124]

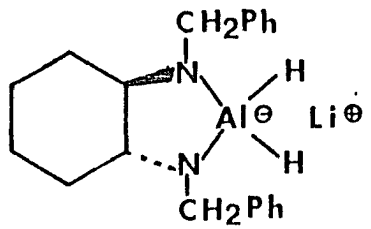
The degree of asymmetric induction of propiophenone by LAH reagents modified with the two chiral decahydroquinoxalines is so small that detailed interpretation may not be appropriate. However, the one observation that both isomers appear to give the reduced alcohol having an (S)-configuration, whereas DBDACH-LAH reagent gives the alcohol with (R)-configuration, is interesting.

The very low asymmetric induction by the DPDHQ*-LAH reagents may be indicative of various opposing factors inherent in such reagents. It has been noted with the aminodiol-LAH reagents studied previously that when more than one chiral center is present in a modifier, the chiral centers can enhance the stereoselectivity by reenforcing each other's influence, or they can act in opposition thus decreasing the stereoselectivity. The increase or decrease may be more than a simple additive effect.[117,119] In the present case the additional DPDHQ* centers may be acting against the induction due to the centers in their DACH portions.

There are, however, other rationalizations worth noting. In the reaction of DBDACH with LAH, a reactive intermediate dihydride (shown in Fig. 44) is expected to be formed. With trans-DPDHQ*, it is unlikely that aluminum-bridging of two nitrogens would take place. The trans-DPDHQ* ring system is analogous to that of a trans-decalin system and is very rigid. It is most likely that the two nitrogen lone pairs are diaxial, and that the two hydrogens are diequatorial. In this conformation, a single LAH cannot react with both secondary amino groups. Both the diequatorial positions and the diaxial positions are pointing in different directions in the trans-fused cyclohexane chair conformation. Inspection of molecular models suggests that although the two nitrogens can be forced into a position so that aluminum-bridging is possible in a boat-like conformation, the resulting structure is under substantial strain. In this structure, nitrogen lone pairs are still pointing outside in opposite directions, preventing coordination to one lithium cation by both nitrogens. While the chiral decahydroquinoxalines used in this study are interesting compounds, they appear to

Figure 44

Intermediate Dihydride




be poorly designed as LAH modifiers.

Since trans-DPDHQ* has a structural feature of diisopropylamine, its lithium amide may be an interesting chiral equivalent of LDA and may be a useful reagent in some base-catalyzed asymmetric reactions.[144-145]

# V: EXPERIMENTAL SECTION

## General Methods

(1) Melting points (mp): Melting points under 250°C were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Melting points over 250°C were determined on a hot-stage apparatus and are uncorrected.

(2) Boiling points (bp): Reported boiling points are those observed during distillation and are uncorrected.

(3) Infrared Spectra (IR): IR spectra were recorded on a Perkin-Elmer 283B infrared spectrophotometer.

(4) Proton nuclear magnetic resonance spectra ($^1$H NMR): $^1$H NMR spectra were recorded on a Varian EM 360A spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from internal tetramethylsilane or sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) unless otherwise indicated. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants (J) are reported in hertz.

(5) $^{13}$C nuclear magnetic resonance spectra ($^{13}$C NMR): $^{13}$C NMR spectra were obtained on a JEOL FX-90Q FT NMR spectrometer with the assistance of Ms. K. Gallagher. Unless otherwise indicated, chemical shifts are reported in ppm downfield from tetramethylsilane as an internal standard.

(6) Optical rotation: Optical rotation was determined on a Carl Zeiss photoelectric precision polarimeter with a 0.2- or 0.5-dm cell. Optical purity (o.p.) of a compound was calculated from the reported maximum

rotation for the compound.

(7) Elemental analyses (CHN): Elemental analyses were performed on a Perkin-Elmer 240B elemental analyzer by Ms. D. Cardin.

(8) Mass spectra: Mass spectra were obtained on a Hitachi-Perkin-Elmer RMU-6E mass spectrometer by Mr. W. Dotchin.

(9) Thin layer chromatography (TLC): TLC was performed on precoated neutral and basic alumina plates from E. Merck Co.

(10) Gas chromatography analyses (GC): GC analyses were performed on a Varian Aerograph Model 90-P gas chromatograph coupled to a Sargent-Welch Model SRG recorder equipped with a Disc integrator. Ketones and alcohols were analyzed on 11 ft x 0.25 in. 5% Zonyl E-7 on 80/100 mesh Chromosorb G column, and amines, on 12 ft x 0.25 in. 10% Carbowax 20M + 5% KOH on 80/100 mesh Chromosorb W column with helium as a carrier.

(11) Materials: The chemicals and solvents used in this work were obtained from commercial sources and were used as received unless otherwise noted.

(12) Dry solvents: Dry diethyl ether was obtained by distillation from benzophenone ketyl or from LAH under nitrogen and was used immediately. Dry THF was obtained by distillation from $CaH_2$, then from benzophenone ketyl under nitrogen and was used immediately.

(13) Reactive metal hydride reductions: All glassware was oven-dried or flamed and cooled under nitrogen. All transfers in asymmetric reductions were made under nitrogen with stainless steel needle or syringe. Solid LAH was weighed out under nitrogen in a glovebag.

(14) Percent enantiomeric excess (% e.e.): The % e.e. of an asymmetric reduction product was determined by dividing the observed

rotation by the literature value reported for optically pure material, then multiplied by 100. In cases where propiophenone was incompletely reduced, the maximum rotation for the carbinol containing a known amount of ketone was determined using a previously prepared correction curve.[146]

(15) Standardization of $LiBH_4$ solutions[147]: With a dry, lubricated syringe, an accurately measured amount (1.0 mL) of ether or THF solution of $LiBH_4$ was injected into a hydrolysis flask containing glycerol-water (1:1 v/v). The volume of hydrogen gas evolved was measured by the displacement of water in a buret. From the observed temperature and pressure and the measured gas volume, the hydride concentration was calculated. The hydrolysis was repeated several times until consistent results were obtained.

## Reactions

### Separation of cis/trans-DACH Isomers

(1) Monohydrochloride method: An HCl-methanol solution (33 mL of 16.7% w/v) was added to a solution of a DACH mixture (8.5 g, 75 mmol*; 97% pure, cis/trans ratio 55:45) in methanol (50 mL) with stirring and cooling in an ice-water bath under nitrogen. The solution was allowed to warm to room temperature and stirred for 36 h. The solvent was removed under reduced pressure (Rotavapor) and the residue was recrystallized from 95% ethanol (50 mL) to yield pale yellow solid (Crop 1: 1.39 g, cis/trans ratio 13:87; Crop 2: 0.8 g, cis/trans ratio 4:96): mp 222-224°C, decomp; $^{13}C$ NMR ($D_2O$, ext $Me_4Si$) 23.3 (cis), 26.5 (trans), 30.2 (cis), 34.5 (trans), 52.8 (cis),

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* Calculation is based on treating the DACH mixture as if it were chemically pure.

57.2 (trans).

Anal. Calcd for $C_6H_{14}N_2 \cdot 2HCl$: C, 38.52; H, 8.62; N, 14.97. Calcd for $C_6H_{14}N_2 \cdot HCl$: C, 47.84; H, 10.02; N, 18.59. Found: C, 47.73; H,10.54; N, 18.97.

Monohydrochloride of DACH is hygroscopic and decomposes in air upon standing overnight.

The mother liquor was evaporated to dryness (Rotavapor, then in vacuo) and the residue was dissolved in abs methanol (10 mL) and diluted with ether (50mL). The resulting dark brown solution was allowed to stand in the refrigerator for 3 d to yield 1.65 g of a light brown, brittle solid. $^{13}C$ NMR spectrum has shown the solid to be a mixture of cis/trans-DACH monohydrochloride (cis/trans ratio 76:24).

(2) Ni Complex Method[13]: To a solution of a DACH mixture (25 g, 220 mmol*; 97% pure) in abs methanol (160 mL), a solution of $NiCl_2 \cdot 6H_2O$ (26 g, 110 mmol) in abs methanol (440 mL) was added and the mixture was stirred for 2 h. The yellow solid was collected by filtration, washed with methanol and dried in vacuo to yield Ni(cis-DACH)$_2Cl_2$ (19.7 g, 97% based on cis/trans ratio 55:45). The filtrate was treated with 4 N HCl (50 mL) and the pH was adjusted to 4-6 by pH paper with 15% NaOH. Upon standing, violet solid deposited. The solid was filtered, washed with water and dried in vacuo to yield Ni(trans-DACH)$_2Cl_2 \cdot 2H_2O$ (11.6 g, 61%).

Ni complex of cis-DACH (7.9 g) was suspended in water (150 mL) and treated with 6 N HCl (15 mL). The solution was taken to dryness (Rotavapor) and the residue was repeatedly washed with abs ethanol and dried in vacuo to give white cis-DACH sulfate (8.2 g, 87%). Free

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* See footnote on p 86.

diamine was obtained by treating the water (25 mL) slurry with 25% NaOH (20 mL) and extracting the mixture with chloroform (5 x 30 mL). The combined organic layers were dried ($K_2CO_3$) and evaporated (Rotavapor), and the residue was distilled with a short path apparatus to yield a colorless liquid (3.11 g, 62% from Ni complex): bp 31-32°C (0.2 mmHg) [ Lit.[13] bp 39-41°C (2 mmHg)].

DACH Resolution

Following procedures are typical of the steps used in the resolution of a commercial DACH mixture.

(1) (-)-(R,R)-1,2-Diaminocyclohexane[25]: A solution of a DACH mixture (960 mL, 7.83 mmol*; 85% pure, cis/trans ratio 40:60 by $^{13}C$ NMR) in water (1.6 L) was heated to 90°C and (+)-tartaric acid (600 g, 4.00 mol; Aldrich Gold Label$^{TM}$) was added in small portions with stirring, followed by glacial acetic acid (400 mL, 7 mol) at such a rate as to keep the solution near boiling. The thick mixture was allowed to cool to room temperature with mechanical stirring. The solid was collected by filtration, washed with cold water (300 mL) and cold 95% ethanol (800 mL), dried and recrystallized from water (4.3 L) to yield 342 g of white crystals. Free diamine was recovered by dissolving the tartrate in an aqueous NaOH solution (1 L of 50%). The organic layer was separated and distilled under nitrogen through a 4 in. Vigreux column at an aspirator pressure to obtain a clear hard solid (101.1 g, 99% o.p.): bp 86-88°C (23-24 mmHg);[ Lit.[12] bp 71-73°C(8 mmHg)]; $[\alpha]_D^{22}$ -41.2° (c 8.57, benzene) [ Lit.[12] $[\alpha]_D^{22}$ -41.5°].

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* See footnote on p 86.

(2) (+)-(S,S)-1,2-Diaminocyclohexane: In the same manner as above, 294 g of (S,S)-DACH tartrate was obtained from a DACH mixture (960 mL, 7.83 mol*; 85% pure) and (-)-tartaric acid (600 g, 4.0 mol; Alfa). Free diamine was continuously extracted with benzene for 5.5 d from the aqueous solution of the tartrate to which NaOH (400 g) and NaCl (400 g) were added. The benzene solution was concentrated under reduced pressure (Rotavapor) and the product was distilled under an aspirator pressure to yield a colorless solid (48.5 g, 98.8% o.p.): bp 90-92.5°C (31-32 mmHg); $[\alpha]_D^{22}$ +41.0° (c 7.44, benzene).

Eschweiler-Clarke N-Methylation[91]

(1) Procedure A[92]: To stirred formic acid (48.4 g, 1.0 mol) cooled in an ice-water bath, a DACH mixture (11.4 g, 100 mmol*) was added slowly under nitrogen, followed by an aqueous formaldehyde (45 mL, 600 mmol of 37%) added at once. The reaction mixture was heated to 90-95°C in an oil bath for 24 h.** 4 N HCl (100 mL) was added to the solution and the mixture was evaporated to dryness (Rotavapor, at 90°C). The dark brown viscous oil was taken up in water (70 mL) with cooling; the solution was made basic with 18 N NaOH (50 mL); and the layers were separated. The aqueous layer was extracted with benzene (4 x 100 mL); the combined organic layers were dried ($K_2CO_3$), and concentrated; and the residue was distilled through a 4 in. Vigreux column to give a colorless liquid (14.0 g, 82%): bp 42-48°C (0.35-

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* See footnote on p 86.

** Heating the reaction mixture in an oil bath at room temperature to the reflux temperature, rather than in a hot oil bath as in the literature method (Ref 92), avoids excessive foaming and the need for an over-sized reaction flask as well as the need to cool the mixture at the start of the gas evolution to control the reaction rate.

0.4 mmHg).

$^{13}C$ NMR and GC analyses of the product have shown that the N-tetramethylation of cis-DACH was incomplete.

(2) Procedure B: A DACH mixture (11.4 g, 100 mmol*; 20% unknown, 35% HMDA, 16% cis-DACH, 31% trans-DACH) was refluxed with formic acid (48.4 g, 1.0 mol) and an aqueous formaldehyde solution (45 mL) for 7.5 d at 95-100°C. After the workup and distillation, a colorless liquid (14.3 g, 84%)was obtained: bp (1.0-1.5 mmHg). There was a substantial amount of dark brown pot-residue remaining after the distillation. This is indicative of the decomposition of HMDA during the prolonged refluxing period, since the product showed a marked decrease of HMDA (down to 28% from 33%). A 2-methyl-1,5-diamino-hexane structure was assigned to the second impurity present in the starting DACH mixture by $^{13}C$ NMR and mass spectra of its tetramethyl derivative obtained by preparatory scale GC: mass spectrum, m/z 172 ($M^+$); $^{13}C$ NMR ($CDCl_3$) 10.44, 24.53, 29.77, 35.41, 45.59, 46.03, 57.64, 64.40.

Anal. Calcd for $C_{10}H_{24}N_2$: C, 69.70; H, 14.04; N, 16.26. Found: C, 69.58; H, 14.34; N, 16.08.

(3) Procedure C: To stirred, cold formic acid (4.84 g, 100 mmol), cis-DACH (1.14 g, 10 mmol) was added, followed by an aqueous formaldehyde solution (4.5 mL, 60 mmol) added at once. The reaction mixture was heated to 100°C in an oil bath for 5 d. Fresh portions of formaldehyde (0.5 mL) were added after 30 h and 55 h. The solution was treated with 4 N HCl (10 mL) and taken to dryness (Rotavapor, at 90°C). The dark brown residue was dissolved in water (17 mL), then

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* See footnote on p 86.

basified with 18 N NaOH (10 mL), and extracted with benzene (4 x 25 mL); the combined organic layers were dried ($K_2CO_3$) and concentrated (Rotavapor); and the residue was distilled to yield a clear liquid (0.73 g, 43%): bp 62-63°C (1.25-1.5 mmHg). The low yield was caused by excessive bumping and foaming during the distillation and it took four attempts to obtain a clear liquid. Both GC and $^{13}C$ NMR analyses of the product showed no trace of TriMDACH.

(4) Timed Reaction 1: The same DACH sample and procedure as in (1) were used. A 15-mL portion of aliquot was withdrawn at 3 h, 6 h, 24 h, 2 d, and 4 d and each aliquot was worked up separately and analyzed by $^{13}C$ NMR and GC.

(5) Timed Reaction 2: In this reaction, aliquots were withdrawn at the following time intervals: 12 h, 18 h, 1.5 d, 2.5 d, and 6.5 d.

A sample of N,N,N'-trimethyl-cis-1,2-diaminocyclohexane (cis-TriMDACH) was obtained by preparatory scale GC: $^{13}C$ NMR ($CDCl_3$) 18.96, 25.25, 25.49, 27.48, 34.72, 43.21, 55.78, 67.53.

N,N'-Dibenzyl-trans-1,2-Diaminocyclohexane (DBDACH)

(-)-(R,R)-DACH (7.79 g, 68.2 mmol; 99% o.p.) was placed in a round-bottomed flask with benzaldehyde (14.8 g, 137 mmol, 98% pure), a catalytic amount of p-toluenesulfonic acid and toluene (250 mL). The mixture was refluxed for 2 h until the theoretical amount of water (2.5 mL) was collected in a Dean-Stark trap. The solvent was removed under reduced pressure (Rotavapor, then in vacuo) to give N,N'-dibenzylidine-trans-1,2-diaminocyclohexane (19.8 g, quantitative): mp 96-98°C; IR (KBr) 1645 $cm^{-1}$ (C=N); $^1H$ NMR ($CDCl_3$) $\delta$ 1.80 (broad, 8H), 3.45 (broad, 2H), 7.15-7.83 (m, 10H), 8.25 (s, 2H); $^{13}C$ NMR ($Me_2SO$-$d_6$) 23.93, 32.58, 73.03, 127.52, 128.37, 130.19,

136.04, 159.91.

The crude product was used in the next step without further purification.

To a solution of diimine (18.94 g, 65.2 mmol) in methanol (200 mL) at 20-23°C (water bath), a cold aqueous solution of $NaBH_4$ (6 g in 90 mL) was added with a capillary dropper over 25 min with stirring. The mixture was stirred for an additional 1 h under nitrogen. The excess hydrides were destroyed with 4 N HCl (50 mL) and the mixture was made strongly basic and extracted with ether (4 x 100 mL). The combined organic phases were dried ($K_2CO_3$) and evaporated to dryness (Rotavapor). The residue was distilled with a short path apparatus to give a colorless liquid ( 13.63 g, 71%): bp 213-214°C (0.7 mmHg); IR (neat) 3305 $cm^{-1}$ (N-H); $^1H$ NMR ($CDCl_3$) $\delta$ 0.6-2.5 (broad, 12H), 3.78 (AB q, 4H), 7.3 (broad s, 10H); $^{13}C$ NMR ($CDCl_3$) 25.01, 31.55, 50.88, 60.89, 126.59, 127.94, 128.20, 141.16; $[\alpha]_D^{22}$ -88.1° (3% methanol).

Anal. Calcd for $C_{20}H_{24}N_2$: C, 81.59; H, 8.90; N, 9.51. Found: C, 81.52; H, 9.00; N, 9.39.

2,3-Diphenyl-trans-Hexahydroquinoxaline (DPHHQ)

Benzil (86.5 g, 410 mmol) and a DACH mixture (50 mL, 410 mmol*; 85% pure) were dissolved in benzene (345 mL) and refluxed under nitrogen for 4 h and water was collected in a Dean-Stark trap. Upon standing for 4 d at room temperature, the solution deposited bright yellow solid. The solid was collected by filtration, washed with cold benzene and dried to give 21.4 g of Crop 1: mp 165-167°C, decomp. The filtrate was concentrated and upon standing deposited 25.8 g of

* See footnote on p 86.

Crop 2: mp 161-167°C. Crop 2 was recrystallized twice from abs ethanol to give yellow needles (17.2 g): mp 171-172°C; $^{1}H$ NMR ($CDCl_3$) $\delta$ 1.0-3.2 (broad, 10H), 7.28 (broad, 10H); $^{13}C$ NMR ($CDCl_3$) 25.43, 33.49, 59.57, 127.98, 129.41, 137.80, 159.65.

Anal. Calcd for $C_{20}H_{20}N_2$: C, 83.30; H, 6.99; N, 9.71. Found: C, 83.57; H, 7.04; N, 9.65.

(R,R)-2,3-Diphenyl-trans-Hexahydroquinoxaline (DPHHQ*)

(-)-(R,R)-trans-DACH (27.38 g, 240 mmol; 99% o.p.) and benzil (50.4 g, 240 mmol) were dissolved in benzene (250 mL) and refluxed for 6 h until the theoretical amount of water (8.5 mL) was collected in a Dean-Stark trap. The solvent was removed under reduced pressure (Rotavapor, then in vacuo) and the residue was recrystallized from abs ethanol (1.8 L) to afford bright yellow needles (63.1 g, 91%): mp 189-190°C; $^{13}C$ NMR ($CDCl_3$) 25.49, 33.56, 59.63, 128.05, 129.41, 137.86, 159.72; $[\alpha]_D^{22}$ -290° (c 1.6, toluene).

Anal. Calcd for $C_{20}H_{20}N_2$: C, 83.30; H, 6.99; N, 9.71. Found: C, 83.11; H, 7.01; N, 9.61.

Reduction of DPHHQ and DPHHQ*

(1) $NaBH_4$ reduction of DPHHQ - Method A: To a stirred solution of DPHHQ (9.00 g, 31.2 mmol) in methanol-toluene (200 mL, 1:1 v/v), a cold aqueous solution of $NaBH_4$ (3.00 g in 50 mL) was added by a capillary dropper over 50 min. After stirring for an additional 2 h, the excess hydride was destroyed with 4 N HCl (50 mL) with cooling in an ice-water bath. The solid formed was collected and dried to give 4.07 g of material which had no mp below 300°C and was insoluble in water and in most organic solvents. Elemental analysis of this crude

material gave a result consistent with the dihydrochloride salt of the expected reduction product.

Anal. Calcd for $C_{20}H_{26}N_2Cl_2$: C, 65.75; H, 7.17; N, 7.67. Found: C, 63.23; H, 6.90; N, 7.53.

The solid was wetted with water (100 mL) and vigorously stirred with 50% NaOH (50 mL) and $CH_2Cl_2$ (50 mL) until two clear layers resulted. The layers were separated; the aqueous layer was extracted with $CH_2Cl_2$ (3 x 150 mL); the combined organic layers were dried ($K_2CO_3$); and the solvent was removed under reduced pressure (Rotavapor) to give 3.90 g of a pale yellow viscous oil which solidified upon standing. The recrystallization from ethanol-water (35 mL, 4:3 v/v) gave a colorless solid (2.04 g): mp 113-115°C; $^1$H NMR ($CDCl_3$) $\delta$1.23-2.03 (broad, 12H), 2.47-2.97 (broad, 2H), 3.87 (s, 2H), 7.17 (s, 10H); $^{13}$C NMR ($CDCl_3$) 24.96, 31.85, 61.63, 68.56, 127.07, 127.76, 128.07, 141.50. This material was designated as trans-2,3-diphenyl-trans-decahydroquinoxaline (t/t-DPDHQ).

Two layers of the filtrate from the reaction mixture were separated. The aqueous layer was made strongly basic with 50% NaOH (30 mL) and extracted with ether (3 x 200 mL). The combined organic layers were dried ($Na_2SO_4$) and the solvent was removed under reduced pressure (Rotavapor). The residue was dissolved in ether and re-dried ($Na_2SO_4$). The removal of the solvent yielded 4.75 g of a dark brown liquid which solidified upon standing. $^1$H NMR showed broad peaks in the alkyl region and complex patterns in the aromatic region. From the presence of a singlet at $\delta$ 3.83 and two doublets at $\delta$ 4.27 and 4.67, this material was determined to be a mixture of two diastereomers of DPDHQ (t/t and c/t) and the starting DPHHQ. No suitable solvent was

found for the fractional recrystallization of this material. The separation of three components by TLC on neutral and basic alumina was also unsuccessful.

(2) $NaBH_4$ reduction of DPHHQ - Method B: To a stirred solution of DPHHQ (1.00 g, 3.47 mmol) in abs methanol (200 mL), solid $NaBH_4$ (2.00 g) was added in small portions over 30 min. An additional methanol (50 mL) was used to wash down the solid on the side of the flask. The reaction mixture was kept near 25°C in a water bath and stirred for an additional 2.5 h, then treated with 4 N HCl (50 mL), and concentrated (Rotavapor) to about 75 mL. The white solid formed was collected by filtration and washed with water (25 mL) and ether (25 mL). The filtrate and the water wash were combined and extracted with ether (3 x 50 mL). The aqueous layer was made strongly basic with 50% NaOH (25 mL); the previously collected white solid was added to it; and the mixture was stirred vigorously with $CH_2Cl_2$ (100 mL) until two clear layers resulted. The layers were separated; the aqueous layer was extracted with $CH_2Cl_2$ (2 x 50 mL); the combined organic layers were dried ($K_2CO_3$); the solvent was removed (Rotavapor); and the residue was dried in vacuo to give a colorless oil which solidified upon standing (0.87 g, 96%). The product was found to be a mixture of t/t-DPDHQ and c/t-DPDHQ (79% t/t, 21% c/t by $^1H$ NMR). $^{13}C$ NMR spectrum of the product did not show the presence of any other material.

(3) $NaBH_4$ reduction of DPHHQ* - Method C: Optically active DPHHQ* (2.00 g, 6.94 mmol) was reduced with solid $NaBH_4$ (4.00 g) in abs methanol in the same manner as Method B, except that the solid precipitate was worked up separately. The solid fraction (insoluble

fraction) yielded 1.44 g (71%) of the product which was found to contain only the t/t isomer by $^1$H NMR. The workup of the filtrate (soluble fraction) yielded 0.58 g (29%) of the product which contained t/t isomer (10%) and c/t isomer (90%) by $^1$H NMR.

(4) $NaBH_4$ reduction of DPHHQ* - Method D: Optically active DPHHQ* (10.0 g, 35 mmol) was partially dissolved in abs methanol (200 mL) and was reduced with solid $NaBH_4$ (4.0 g) in a manner similar to Method C. The insoluble fraction was worked up separately and the product was recrystallized from methanol-water (3:1 v/v) by allowing the solvent to evaporate slowly over three weeks to yield 5.48 g (54%) of fine needles: mp 65-66°C; $^1$H NMR ($CDCl_3$) $\delta$1.2-2.0 (broad, 10H), 2.5-2.8 (broad, 2H), 3.83 (s, 2H), 7.13 (s, 10H); $^{13}$C NMR ($CDCl_3$) 24.97, 31.86, 61.58, 68.54, 127.08, 127.72, 128.05, 141.44; $[\alpha]_D^{22}$ -75.2° (c 1.14, abs ethanol).

Anal. Calcd for $C_{20}H_{24}N_2$: C, 82.15; H, 8.27; N, 9.58. Found: C, 82.09; H, 8.35; N, 9.55.

The soluble fraction gave 2.31 g (23%) of a mixture of two diastereomeric DPDHQ*.

(5) Reduction with DMA•$BH_3$ in acetic acid: To a stirred suspension of DPHHQ* (2.00 g, 6.94 mmol) in glacial acetic acid (10 mL), a solution of DMA•$BH_3$ (1.02 g, 17 mmol) in glacial acetic acid (10 mL) was added over 10 min with cooling in a cold water bath at 15°C under nitrogen. The mixture was warmed to 60°C for 15 min; then it was cooled in an ice-water bath and diluted with water (100 mL). The solution was treated with 5 M NaOH (60 mL) and the mixture was stirred with $CH_2Cl_2$ (150 mL) until two clear layers resulted. The layers were separated; the aqueous layer was extracted with $CH_2Cl_2$ (2

x 150 mL); the combined organic layers were dried ($K_2CO_3$); and the solvent was removed (Rotavapor) to give a pale yellow oil (1.83 g, 91%). The product contained 20% t/t-DPDHQ* and 80% c/t-DPDHQ* by $^1H$ NMR.

(6) Reduction with DMA•$BH_3$ in THF: To a stirred solution of DPHHQ* (2.00 g, 6.94 mmol) in THF (75 mL), a solution of DMA•$BH_3$ (0.82 g, 13.9 mmol) in THF (25 mL) was added dropwise over 15 min under nitrogen with cooling in a water bath (20°C). The solution was stirred for 5 d at room temperature and it was refluxed for 24 h. The solution was still strongly colored indicating that very little reduction had taken place. The solution was cooled in an ice-water bath and 4 N HCl (20 mL) was added slowly. There was an immediate color change and a gas evolution was evident. The mixture was stirred for an additional 2 h under nitrogen and it was allowed to warm slowly to room temperature. The solid formed was separated and the insoluble fraction and soluble fractions were worked up separately. They were recombined and the diastereomer ratio of the product was determined by $^1H$ NMR.

(7) Reduction with $NaBH_3CN$: DPHHQ* (1.00 g, 3.47 mmol) was suspended in glacial acetic acid (25 mL) and the mixture was cooled in a cold water bath (10°C). $NaBH_3CN$ (2.00 g, 35 mmol) was added in two portions. The mixture was stirred for 2 h under nitrogen and it was diluted with water (75 mL) and made strongly basic with 5 M NaOH. The standard workup gave a yellow oil (0.89 g, 88%). $^1H$ NMR spectrum of the product has shown that it contained 20% t/t isomer and 80% c/t isomer.

(8) Reduction with $BH_3 \cdot THF$: In a dry round-bottomed flask, was placed a solution of DPHHQ* (1.00 g, 3.47 mmol) in dry THF (80 mL) under nitrogen. The reaction flask was cooled in an ice-water bath and a 1 M $BH_3 \cdot THF$ solution (7 mL) was added at once from a dry syringe. The solution was stirred at room temperature for 24 h. The standard workup gave a clear, viscous oil (0.99 g, 98%). The product was found to contain 74% c/t siomer and 26% t/t isomer by $^1H$ NMR.

(9) Reduction with Na° in ethanol: DPHHQ* (592 mg, 2.05 mmol) was partially dissolved in dry abs ethanol (100 mL; stored over 3 Å molecular sieves) and the mixture was cooled in an ice-water bath. Sodium metal (0.5 g, 20 mmol) was added in two portions under nitrogen. When the gas evolution became smooth, the cooling bath was removed and the mixture was stirred until all the sodium metal had been consumed. The standard workup resulted in the quantitative recovery of the starting material.

(10) Reduction with $LiBH_4$ in ether: In a dry flask, $NaBH_4$ (0.95 g, 25 mmol), anhydrous LiBr (2.17 g, 25 mmol) and dry ether (50 mL) were placed and the mixture was stirred under nitrogen at room temperature for 3 d. The hydrolysis of the solution indicated that a very little $LiBH_4$ had been formed. $LiBH_4$ solution (14 mL) was added to a solution of DPHHQ* (1.00 g, 3.47 mmol) in dry ether (100 mL) along with $NaBH_4$ (0.26g, 6.87 mmol) and LiBr (0.60 g, 6.91 mmol). The mixture was stirred for 5 d at room temperature and refluxed for 8 h. The mixture, diluted with water (25 mL) and 4 N HCl (10 mL), was stirred for 2 d. The standard workup gave a product containing mostly benzil and DACH and very little DPDHQ*.

(11) $LiBH_4$ reduction in THF: Anhydrous LiBr (2.17 g, 25 mmol) and $NaBH_4$ (0.95 g, 25 mmol) in dry THF (40 mL) were stirred at room temperature under nitrogen for 48 h. The hydrolysis of an aliquot gave the $LiBH_4$ solution to be 0.4 M. To a stirred solution of DPHHQ* (1.0 g, 3.5 mmol) in dry THF (75 mL) cooled in an ice-water bath, a standardized $LiBH_4$ solution (20 mL, 8 mmol) was added. The mixture was stirred for 3 d at room temperature. More $LiBH_4$ solution (15 mL) was added and the solution was refluxed for 24 h. It was still yellow, indicating an incomplete reduction. The standard workup yielded 0.63 g (62%) of material containing 39% c/t isomer and 61% t/t isomer. 0.10 g of benzil was also recovered.

(12) LAH reduction - Method D: LAH (310 mg, 7.76 mmol) was added to dry ether (75 mL), and the mixture was stirred for 0.5 h under nitrogen with cooling in an ice-water bath. A solution of DPHHQ* (1.00 g, 3.47 mmol) in dry ether (100 mL) was added over 20 min. The mixture was stirred for 24 h at room temperature. The standard workup gave 0.99 g (98%) of the product containing 98% c/t isomer and 2% t/t isomer.

(13) LAH reduction - Method E: DPHHQ* (5.50 g, 19.1 mmol) was reduced with LAH (1.50 g, 37.6 mmol) in dry ether (250 mL) in a manner similar to Method D. Solid DPHHQ* was added directly to the LAH suspension with a Gooch tubing. The reaction mixture was stirred at room temperature for 24 h, refluxed for 24 h, and again stirred at room temperature for an additional 3 d at which time it turned to grey from the initial green color. The standard workup resulted in 5.50 g (98%) of a crude product. The crude product was dissolved in ether (100 mL) and HCl gas was bubbled through. The solid formed was

collected by filtration and washed thoroughly with ether and dried in vacuo to yield 6.13 g of dihydrochloride salt. It was dissolved in methanol (60 mL) and re-precipitated with an equal volume of ether. The solid was washed with cold methanol-ether (1:1 v/v) and air-dried to yield 4.36 g of the salt.

Anal. Calcd for $C_{20}H_{26}N_2Cl_2$: C, 65.75; H, 7.17; N, 7.67. Found: C, 65.50; H, 7.12; N, 7.61.

Dihydrochloride salt was dissolved in water (50 mL) and the solution was treated with NaOH pellets until strongly basic, resulting in formation of white solid. The mixture was vigorously stirred with ether (50 mL) until two clear layers resulted. The layers were separated and the aqueous layer was extracted with ether (3 x 50 mL). The combined organic layers were dried ($Na_2SO_4$); the solvent was removed (Rotavapor); and the residue was dried in vacuo to yield 3.35 g of colorless solid: mp 94-95°C; $^1$H NMR ($CDCl_3$) $\delta$1.0-2.2 (broad, 10H), 2.4-3.1 (broad, 2H), 4.20 (d, J = 7, 1H), 4.67 (d, J = 7, 1H), 7.1-7.8 (m, 10H); $^{13}$C NMR ($CDCl_3$) 24.91, 32.19, 32.32, 53.58, 63.14, 64.18, 126.55, 126.94, 127.46, 127.79, 130.06, 141.57, 141.90; $[\alpha]_D^{23}$ +174.2° (c 1.31, abs ethanol).

Anal. Calcd for $C_{20}H_{24}N_2$: C, 82.15; H, 8.27; N, 9.58. Found: C, 82.06; H, 8.27; N, 9.35.

Asymmetric Reduction of Propiophenone

The following procedure is exemplary.

Dry ether (100 mL) was placed in a 250-mL, three-neck round-bottomed flask, flushed with nitrogen and equipped with a magnetic stirring bar, a reflux condenser and a septum and cooled in an ice-water bath. LAH (0.24 g, 6.0 mmol) was added, followed by an

additional 50 mL of dry ether to wash the last traces of LAH into the flask. The resulting suspension was stirred for 0.5 h. A solution of the diamine (6.2 mmol) in dry ether (25 mL) was added over 5 min by a syringe and the mixture was stirred for 1 h at room temperature. The mixture was cooled in a dry ice-acetone bath and a solution of propiophenone (0.67 g, 5 mmol) in dry ether (25 mL) was added with a syringe. The reaction mixture was allowed to warm slowly to room temperature and was stirred for 18 h. The mixture was hydrolyzed with water (50 mL); the layers were separated; the organic layer was washed with 1 N HCl (3 x 50 mL) and water (1 x 50 mL).* The ether layer was dried ($Na_2SO_4$) and concentrated (Rotavapor). The residue was purified by Kugelrohr distillation to yield 0.5 g of a colorless liquid. The product was analyzed by GC for % reduction prior to the measurement of the optical rotation.

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* The combined acid and water wash gave 1.94 g (86%) of the recovered dihydrochloride of t/t-DPDHQ*.

# APPENDIX

# Diaminocyclohexane Analytical Procedure

This analytical method is a gas chromatography method to analyze for Cis - and trans - DCH, and common impurities, HMI, MPMD, and HMDA.

## GC

An isothermal GC equipped for capillary column with inlet splitter and flame ionization detector is satisfactory. An adequate peak integrator should also be used.

## COLUMN

J and W thick film, 1um, DB-5, 30m X 0.252mm. This is a nonpolar stationary phase.

## ANALYSIS CONDITIONS

| | |
|---|---|
| Injection size, | 0.1ul |
| Split ratio, | 100:1 |
| Oven temperature, | 104 deg C |
| Column head pressure, | 11 psi (75 KPa) |
| Injector temperature, | 200 deg C |
| Detector temperature, | 250 deg C |

## RETENTION TIMES

| | |
|---|---|
| Hexamethyleneimine, HMI | 3.40 min |
| Trans-1,2-diaminocyclohexane, t-DCH | 7.30 min |
| 1,5-Diamino-2-Methylpentane, MPMD | 7.56 min |
| Cis-1,2-diaminocycohexane, c-DCH | 7.92 min |
| Hexamethylenediamine, HMDA | 9.32 min |

## REPORTING RESULTS

If weight percent is desired, the area percent results must be corrected for response differences. The response factors for all of the compounds are the same within 2% except for HMI. To correct HMI, multiply HMI area percent by 0.868 and normalize this and the other area percent values. This will give results as weight percent.

DCH Analytical Procedure
Page 2

COMMENTS

The MPMD is a small peak between the Cis - and trans - DCH. It may be necessary to adjust the oven temperature to move the MPMD out from under either the cis - or trans - DCH.

With the polar amines, it is easy to overload the nonpolar DB-5 column. If poor peak shapes are encountered try reducing injection size.

Because the amines pick up CO2 from the air it is advantagous to wash the syringe with a solvent (e.g. methanol) after each injection.

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